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PLASMA CELL MASTITIS—A LESION SIMULATING MAMMARY CARCINOMA

A CLINICAL AND PATHOLOGIC STUDY WITH A REPORT OF TEN CASES

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Eight years ago my associates and I operated in a case of what was believed at the time to be mammary carcinoma. There was present a hard, diffuse mammary tumor. The nipple was retracted. The breast had the peau d'orange appearance typical of carcinoma. The axillary nodes were much enlarged and quite hard. There was no question in the minds of the several clinicians who examined this patient as to the diagnosis of carcinoma, as nearly all of the classic diagnostic signs were present. A radical amputation was performed. Examination of the specimen later in the laboratory, to our complete surprise and chagrin, revealed no cancer. Dr. Ewing, after making a careful study, rendered the diagnosis of "plasma cell mastitis," a term entirely new to us. He named this lesion plasma cell mastitis on account of the overwhelming preponderance of the plasma cell. This cell is not prominent in the more common forms of chronic mastitis and other conditions of the breast, except as the occasional stray cell; but in this lesion there are broad sheets of plasma cells. In addition to this, the microscopic slide shows "remarkable atypical proliferation of lining cells of ducts which considerably resembles carcinoma" (Ewing). A subsequent scrutiny of the details of the case left us in somewhat of a quandary as to how to avoid making a similar diagnostic error, provided such a case again came into our hands. During the course of the past eight years ten such cases have come under our observation, and an analysis of these cases has convinced us that this group, difficult of diagnosis for both clinician and pathologist, represents a distinct clinical entity. Our studies of these cases lead us to the conclusion that plasma cell mastitis is a disease of the breast which gives a characteristic history and possesses features which usually make a clinical diagnosis possible even though difficult.

The object of this report is: (*a*) to establish the condition in this group of cases as a distinct clinical disease among mammary lesions, (*b*) to place the diagnosis on a more cleancut basis and (*c*) to prevent performance of grave and possibly unnecessary operations.

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Literature on the subject of mastitis is especially voluminous. This seems, however, to be the first report on this type of mastitis, except the article on the subject to be found in the recent book by Cheatle and Cutler, "Tumours of the Breast," which is based on a study of the ten cases herein reported. The reader is referred to this article.

At times the diagnosis of mammary cancer is easy even for the novice; but at other times it is impossible for one possessing an extensive experience to be sure of the exact nature of the lesion. The difficulty of diagnosis in this group of cases will be emphasized by the fact that six of these ten cases were diagnosed as cancer by several men who have a large experience in the diagnosis of cancer.

In general, the present difficulty with clinicians in arriving at a correct diagnosis of diseases of the breast is that they too quickly conclude that the lesion is cancer, provided one or more of the diagnostic points are present, such as: retraction of the nipple, skin attachment, peau d'orange appearance, hardness and irregularity. They do not give sufficient consideration to the fact that certain benign lesions give some of the signs generally considered to be characteristic of mammary cancer. Since women now present themselves for examination much earlier than previously, the difficulties of diagnosis have greatly increased. It is therefore most important that added consideration be given to each one of the diagnostic points and that the most exact history possible be elicited.

Clinically, the two most common and difficult lesions to be differentiated from cancer are: (*a*) a localized area of chronic mastitis and (*b*) fibro-adenomas in young women.

It may be helpful at this point to give a list of those benign lesions which at times simulate carcinoma and occasionally give one or more of the signs of cancer such as skin attachment, retraction of the nipple, elevation of the breast, peau d'orange appearance or irregularity of the contour of the breast. They are the following: (1) traumatic fat necrosis,[2] (2) plasma cell mastitis, (3) chronic lactation mastitis,[3] (4) subacute inflammatory mass, (5) tuberculous mastitis, (6) gumma[4] and

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1. Cheatle and Cutler: Tumours of the Breast, Philadelphia, J. B. Lippincott Company, 1931, p. 298.

2. Lee, Burton J., and Adair, Frank E.: Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma, Ann. Surg. **72**:189 (Aug.) 1920; A Further Report on Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma, Surg., Gynec. & Obst. **34**:521 (April) 1922; Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma, Ann. Surg. **80**:670 (Nov.) 1924.

3. Cohn, L. Clarence, and Bloodgood, J. C.: Chronic Lactation Mastitis, Suppurative and Non-Suppurative, Am. J. Cancer **16**:487 (May) 1932.

4. Adair, Frank E.: Gumma of the Breast: Its Differential Diagnosis from Carcinoma, Ann. Surg. **79**:44 (Jan.) 1924.

syphilitic mastitis, (7) deep abscess (occasionally), (8) cyst (infrequently), (9) intracannicular fibro-adenoma (rarely), (10) traumatic mastitis and (11) benign lesion such as fibro-adenoma or papillary cyst adenoma lying within the areola.

In this list of eleven benign lesions it is to be noted that seven are of various forms of mastitis. The diagnosis of chronic mastitis of the simple forms (hypertrophic, cystic and fibrous) is usually easy as it is more commonly bilateral and the entire gland is involved. One is able to pick up the breast as a whole, the edge of which is sharply defined and, as has often been said, like the edge of a saucer.

The natural history of plasma cell mastitis should be divided into two stages:

(*a*) The acute phase. Unfortunately, the clinician rarely has the opportunity to examine the patient during this early phase because the acute symptoms such as pain, discomfort and tenderness are of such a mild degree that the patient infrequently seeks medical advice. The lesion does not proceed to abscess formation. There is a mild degree of local heat, tenderness and discomfort. The condition occurs spontaneously in a nonlactating breast. The acute process gradually subsides leaving the breast the seat of a residual, nontender tumor.

(*b*) Residual phase. This phase varies in duration from several weeks to several months after the appearance of the acute phase. The presence of a mass (fig. 1) brings the patient to the physician. He finds that the mass is not tender to palpation; it may be sharply localized or a diffuse thickening; it is firm; there may or may not be a discharge from the nipple; if present, it is watery or creamy and on microscopic examination reveals cellular detritus, mucus and desquamated degenerating lining cells. Pumping the breast with a breast pump produces this discharge over long periods if continued. Edema is frequently present over the tumor or in the dependent portion of the breast, giving the peau d'orange appearance. The nipple is retracted. Enlarged firm axillary nodes are usually present. Acute and subacute inflammatory signs are completely lacking. At this stage the lesion closely simulates mammary carcinoma.

The clinician is practically forced by the preponderance of the multiple signs of carcinoma, to arrive at a diagnosis of cancer unless he carefully considers the preceding history of the case.

Just as it is true that the differentiation of mammary cancer from traumatic fat necrosis [2] is impossible except by a detailed scrutiny of the preceding history of a competent producing injury, so it is true in plasma cell mastitis that one must rely on the antecedent history of inflammation.

As a rule, in our cases, even though the breast was nonlactating (with one exception), there was a history of acute inflammation accompanied by redness, tenderness and discomfort. This is the most important single point in the history. In our later cases we felt capable of making a correct diagnosis. In one of them we correctly suspected the exact pathologic condition for as long as two years; but as so little change took place in the tumor itself, we felt forced to capitulate from our position of frequent observations and operate in order to be certain of our diagnosis. This was before the days when we began to make such valuable use of aspiration [5] and punch [6] biopsy for assistance in diagnosis.

Another of our patients was under observation for two years. We thought the history so typical and the lesion so characteristic that we felt confident of the diagnosis of plasma cell mastitis. This patient was

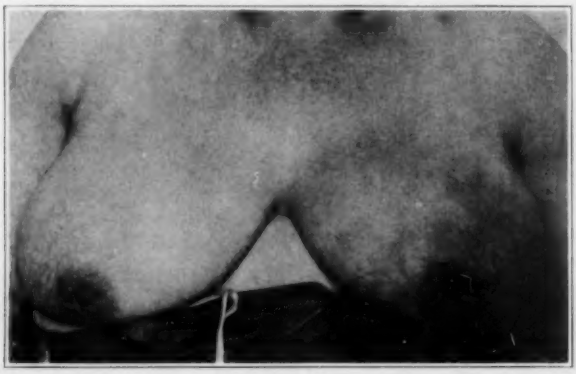

Fig. 1 (case 10).—Photograph showing slight discoloration or duskiness of the left breast; also retraction of the nipple. The affected breast is heavier than the right, and there is a diffuse hard thickening in the outer half and a peau d'orange appearance. One large axillary node was present. It is five and a half years since the only pregnancy. The patient was under observation for two years before operation.

later operated on in another institution in New York City for cancer, the radical amputation being done. The slides were sent to us, and the condition proved to be plasma cell mastitis (fig. 1).

COURSE

It is of great importance and interest to know exactly what happens to the tumor if left alone. In the two foregoing cases, we have had a

5. Martin, Hays E., and Ellis, Edward B.: Biopsy by Needle Puncture and Aspiration, Ann. Surg. **92**:169 (Aug.) 1930.

6. Hoffman, William J.: New Technic and Instrument for Obtaining Biopsy Specimens, Am. J. Cancer **15**:212 (Jan.) 1931.

rare opportunity to study its course. To our surprise practically no change took place for two years. The tumors seem to have no tendency to resolve spontaneously. Even the use of the breast pump over a considerable period had but little influence, in spite of the fact that one could nearly always obtain some secretion from the nipple ducts.

We present no evidence that plasma cell mastitis is a true forerunner of cancer; but, on the other hand, there is no evidence that it is not. In general, it appears to take a long time for the etiologic factors actually to produce a cancer of the breast. No one is certain what would transpire in this particular tumor over a period of ten or fifteen years if left alone. The chemical irritation of the retained puriform material in all likelihood results in the proliferation of the lining epithelium until there are sometimes as many as six or eight rows of hyperchromatic epithelial cells. This would definitely place the lesion in the "precancerous" group in the usual interpretation of that term. We have had the unusual experience of watching two cases for a period of two years without cancer developing, but even so, a reasonable attitude toward this lesion would be to regard it as one capable of later developing into cancer. Provided this assumption is justifiable, it should then be treated as other precancerous lesions, by removing the mass itself and leaving the rest of the breast untouched.

ANALYSIS OF TEN CASES

Age.—The age incidence in the ten cases is from 29 to 44 years. Although it is true that the average age is 36.3 years, which is well below the decade (from 50 to 60 years) when most mammary cancers develop, still any one with experience does not hesitate today to render a diagnosis of mammary cancer in the decade of 30 to 40 years or younger. The average younger age of these patients, therefore, should be of some aid in the diagnosis.

Duration Since Last Lactation.—The duration of time since the last lactation seems to have no bearing on the etiology. In fact, in the majority of instances it was a period of several years since the last lactation. In one case, it was nine years. If the one instance of an actually lactating breast were excluded, the average time since the last lactation would be nearly four years.

Previous Pregnancies.—In no instance did plasma cell mastitis occur in an unmarried woman. With the exception of case 8, in which there was one miscarriage, there was an average of nearly four previous pregnancies in each case. This suggests strongly that improper drainage of the breast has an important bearing on the etiology.

Symptoms.—As a rule, the presence of a lump brought the patient to the physician. In going into the history of the patients, it is interesting

to note that they commonly had previously complained of a pain localized in the region of the lump. Pain was the first symptom noted by the patient, and it was frequently accompanied by localized redness and also at times by a discharge from the nipple. The patients stated that even in the acute stage the breast was not especially tender on palpation. The patient in case 9 had redness and tenderness which subsided under cold applications, leaving a residual hard lump. The lack of symptoms which bother the patient is striking in this disease.

Nipple Discharge.—In seven of the ten cases there was either a spontaneous discharge at the nipple or a discharge produced by gently stroking the breast toward the nipple. As a rule, the material was thick and typical of stagnated dilated ducts. In case 3, either by stroking the breast or by pumping with a breast pump, there was consistently obtained from the identical six ducts a thick creamy material. From the breast of the patient in case 2 a test tube full of creamy material was obtained at the first pumping, and up to the date when a mastectomy was performed we were able to obtain some of this thick material. In case 1, the material was yellow and purulent. The sign of a discharge from the nipple is of definite aid in the diagnosis of plasma cell mastitis.

Weight.—As a rule, the involved breast is heavier than the opposite unaffected breast. This, however, is true of carcinoma and is therefore of no aid in the differential diagnosis from cancer.

Retraction of the Nipple.—This sign is commonly positive in cancer of the breast. In our ten cases of plasma cell mastitis, it was definitely positive in eight (80 per cent), and in two cases the history did not mention this point. It seems to be a more consistent sign in plasma cell mastitis than in mammary carcinoma.

Skin Adherence.—The tumor was adherent to the skin in six of the ten cases (60 per cent). In cases 4, 6 and 9 the sign was very marked.

Peau d'Orange Appearance.—In four of the ten cases a definite statement was made that this sign was positive. No mention is made on this point in several cases.

Tumor.—The mass was always either firm or hard. It varied from a discrete, sharply outlined mass to a firm ill defined but localized process. The largest mass was that in case 3, measuring 8 by 8 by 10 cm. The lesions averaged approximately from 4 to 5 cm. in diameter.

Axillary Nodes.—In eight of the ten cases the axillary nodes were enlarged and hard. In case 8, it is stated that "there is a chain of hard nodes extending from the tail of the breast across the axilla." In case 4, it is stated that "there is a hard mass in the right axilla 4 cm. in diameter." The presence of enlarged hard nodes (80 per cent) is therefore more common than in cancer.

Transillumination Test.—In only two of our cases was this test used. In case 10, the breast was opaque to transillumination; in case 5, the test was negative. This test was not sufficiently used to enable us to state what its value would be in diagnosis.

Preoperative Diagnosis.—In two of our later cases (cases 2 and 10) the correct diagnosis of plasma cell mastitis was made. In case 5, the diagnosis of mastitis nodule was made, and in case 7, tuberculous mastitis. In five cases a positive diagnosis of cancer was rendered; in case 6, the pathologic condition was thought to be carcinoma. In case 9, the case was classified as a primary inoperable mammary carcinoma, and to add to the confusion a roentgenologic report of the chest was returned

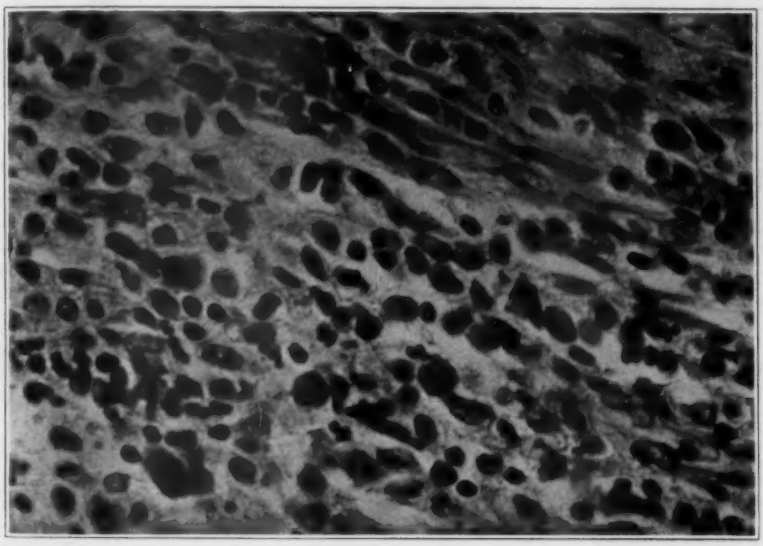

Fig. 2 (case 2).—High power photomicrograph showing infiltration with plasma cells. The cytoplasm is granular with eccentrically placed nuclei.

"evidence of metastasis." In this case several large axillary nodes, a pig-skin appearance, skin attachment, retraction of the nipple and a hard tumor were present. It was a textbook example of a case giving nearly all the classic signs of cancer, and on the signs alone one would have been forced to render such a diagnosis. However, the patient's history stated that "redness and tenderness were present for three weeks, subsiding under cold applications, leaving a hard lump." This important history of a lump residual after a preceding inflammatory process is the only factor that makes diagnosis possible in this disease. This point cannot be overemphasized in the diagnosis of plasma cell mastitis.

Treatment.—In each of the ten cases the diagnosis could have been established and the patient cured by the local removal of the tumor—a

small and simple operation. Instead of this, in eight cases, mastectomy was performed, while in only two local operations were used. The latter was due to the fact that we paid especial attention to the history of a preceding inflammatory process. Since the proper line of treatment rests on a correct diagnosis, it is obvious that the exact diagnosis of this condition will save many patients from an unnecessarily large operation. Incidentally, in statistical studies of end-results it is probable that some "cures" include some cases of plasma cell mastitis.

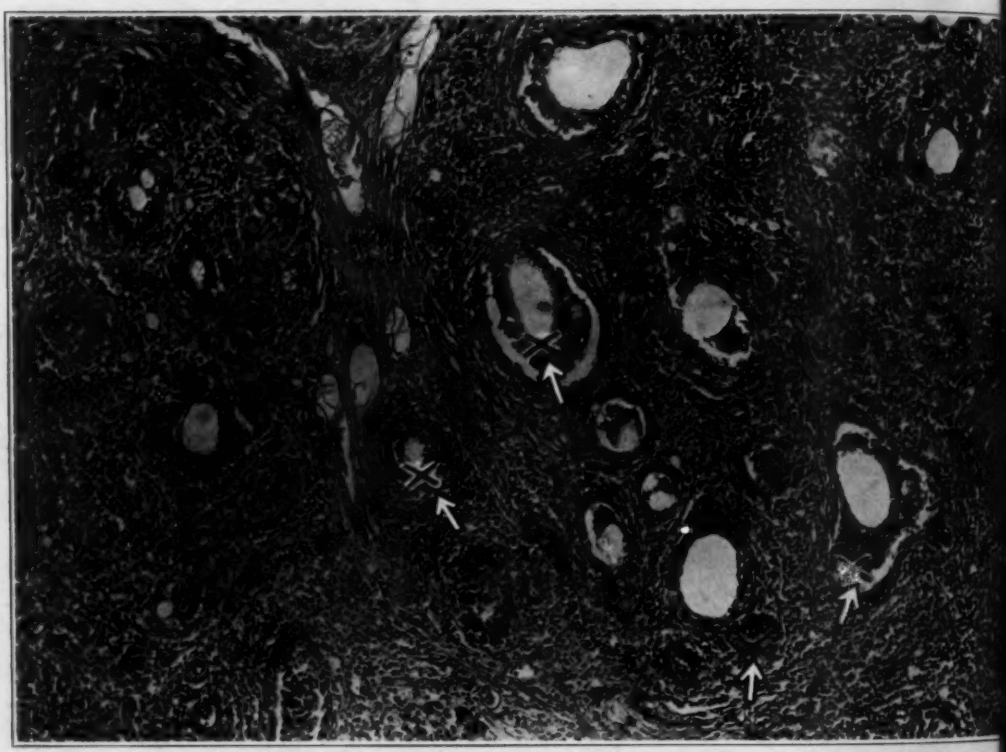

Fig. 3.—Photomicrograph showing the heaping-up of the layers of lining cells characteristic of plasma cell mastitis. Certain ducts indicated by crosses are completely filled with hypertrophic cells suggesting comedocarcinoma.

Pathology.—There are three outstanding characteristics of this lesion: (*a*) Marked infiltration by the plasma cell (fig. 2). This cell is of rare occurrence in lesions of the breast. It has granular cytoplasm with an eccentrically placed nucleus. It is thought by some to be a wandering blood corpuscle that occurs in certain chronic lesions. In plasma cell mastitis the cells occur in broad sheets, invading the ducts, the walls and the interstitial tissues.

(*b*) Proliferation of the cells lining the ducts. They pile up six to ten rows deep, with hyperchromatic epithelium. This gives an appearance at times difficult to distinguish from comedocarcinoma (fig. 3).

(*c*) Formation of giant cells (fig. 4) from these proliferating lining cells. The presence of these giant cells together with their arrangement at times makes differentiation from tuberculous mastitis puzzling.

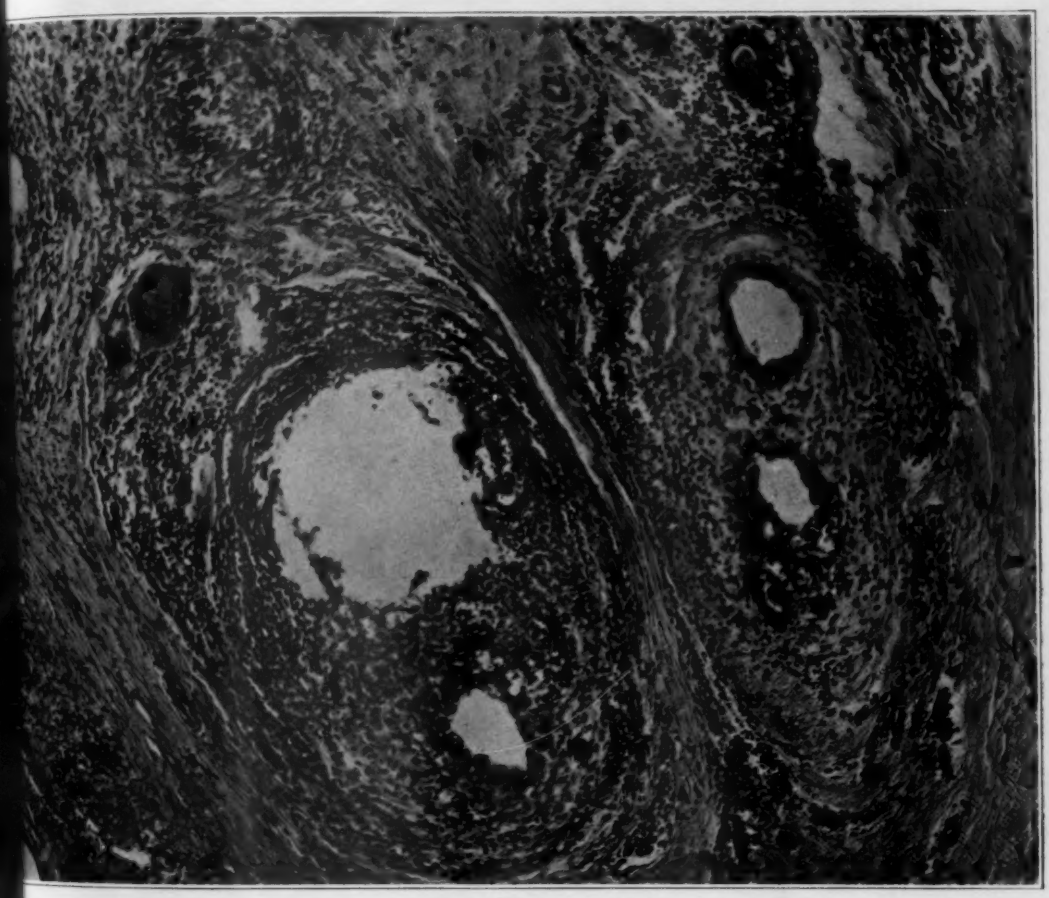

Fig. 4.—Photomicrograph showing a tremendous heaping-up of duct lining cells almost filling the large ducts.

Case 7 presents the clinical appearance of tuberculosis of the breast (fig. 5). An abstract of the ten cases is given here.

The pathologic reports are of such interest and value, especially to pathologists, that Dr. Ewing's exact descriptions are quoted in detail.

Case 1.—A. R., aged 44, had had four children, eight years elapsing since the last lactation. She came for examination on account of a lump in the breast.

There was a purulent yellowish discharge from the nipple. The breast was distorted in shape. The nipple was retracted and fixed. A tumor measuring 6 by 6 by 6 cm. lay behind the nipple. Axillary nodes were present. A preoperative diagnosis of carcinoma was made, and a radical amputation was performed.

"The large ducts are distended with pus and the walls infiltrated with many plasma cells. The prominent feature is the presence of many small ducts moderately filled with pus lined by very hyperplastic and hypertrophic epithelial cells, somewhat resembling beginning carcinoma, except that the cells are not hyperchromatic; about these ducts there is a rich infiltration of plasma cells, but no wide areas of diffuse plasma cell infiltration in this breast. There are many giant cells including fat globules. Extensive hyperplastic lymphadenitis."

CASE 2.—K. S., aged 40, had had five pregnancies, twenty months elapsing since the last one. Although painless to palpation, some sticking pains were experienced in the left breast. On pumping with a breast pump, a large test tube of creamy material was obtained. The left breast was much heavier than the right. The nipple was retracted. There was skin adherence and a peau d'orange appearance. The tumor measured 7 by 8 by 7 cm. Many large hard axillary nodes were present.

Fig. 5 (case 7).—The appearance of a breast with a condition simulating tuberculosis. There is wide area of skin infiltration, retraction of the nipple, discoloration and marked irregularity with a suggestion of an old healed sinus.

There was no elevation of temperature. The leukocyte count was normal. A preoperative diagnosis of plasma cell mastitis was made, and mastectomy was performed.

"This is a typical case of focal and diffuse plasma cell mastitis in which many leukocytes and lymphocytes are mingled with plasma cells. The infiltrated areas represent ducts and measure from 1 mm. to 1 cm. in diameter. The epithelium shows marked hyperplasia but terminates in the formation of many giant cells."

CASE 3.—R. C., aged 44, had had eight pregnancies, two years elapsing since the last lactation. Eight months before she was seen by us she noted a lump in the breast, but felt very slight pain. When the breast was stroked toward the nipple or when it was pumped, a creamy material came through six ducts. The nipple was retracted. A mass was present measuring 10 by 8 by 8 cm., the size of a lemon. Large axillary nodes were present. A preoperative diagnosis of carcinoma was made, and mastectomy was performed.

"This is a rather typical case of plasma cell mastitis. There are broad areas in which the ducts are obliterated by diffuse exudate of plasma cells. The epithelial cells are degenerating, and there are many giant cells containing lipoid material; there are comparatively few polynuclear leukocytes. Most of the epithelial cells

are mingled and lost among the plasma cells. There is moderate reactive fibrosis about some lobules. The giant cells are at times very numerous and somewhat resemble miliary tubercles."

CASE 4.—M. W., aged 40, had had three pregnancies. At the time of examination the breast was lactating, the patient having had a child four weeks previously. Two days before the birth of the child she noted pain in the breast and the presence of a lump. The skin over the lump was red. This was aspirated twice, but only serum was obtained. There was marked skin adherence. A tumor was present measuring 8 by 4 by 4 cm. A mass was present in the right axilla measuring 4 cm. in diameter. The patient was examined by ten physicians, and the diagnosis was made of a probable carcinoma in a lactating breast. A local removal of this mass was made, and a frozen section immediately examined.

"Material received consists of a mass of tissue size of small orange, and containing mostly dense translucent tumor-like tissue surrounded by a zone of fat tissue. The mass has all the density and resistance of carcinoma. On section there are many peculiar ochre yellow points and spots 1 to 3 mm. wide which project prominently as from pressure. These xanthomatoid foci are soft not semifluid, not purulent, but not firm enough for tumor tissue. In the densest portions of tissue there are no chalky streaks, but much of the dense tissue appears cicatricial and very suspicious of carcinoma of rapid growth.

"Microscopic sections show as the main features numerous foci, very cellular and composed of large rounded and polyhedral cells distended with lipoid material and often containing a great many polynuclear leukocytes and miliary abscesses. All these foci contain a great many plasma cells, which infiltrate the tissue widely. These fatty foci are the protuberant xanthomatoid areas mentioned in the gross. The glandular and duct epithelium seems to disappear in the mass of polyhedral cells and plasma cells and nowhere are there any definite foci or sheets of carcinoma cells. Yet in many less altered lobules the acinar cells are rather atypical and hyperchromatic. The outlying tissue contains many breast gland lobules which show the changes of lactation.

"*Diagnosis.*—Subacute suppurative and plasma cell mastitis in a typical case of focal and diffuse plasma cell mastitis."

CASE 5.—C. B., aged 32, had had one child, nine years elapsing since the last lactation. A lump had been present in the right breast for one week. The patient had had some pain in this breast for a month. There was a discharge from the nipple. The ducts all felt thickened. The nipple was markedly retracted. The breasts were asymmetrical, and the right breast was very hard. A small lump measuring 1 by 1 by 1 cm. was present in the right breast. No axillary nodes were present. The transillumination test was negative. A preoperative diagnosis of mastitis was made. The local removal of the mass was performed.

"Specimen consists of a fragment of tissue measuring 4 by 2.5 cm. composed of fat and fibrous tissue. At one point there is an area of denser fibrous structure measuring 0.5 cm. with one or two chalky streaks. Sections of two small ducts show the usual appearance of epithelial proliferation and degeneration with plasma cell infiltration."

CASE 6.—A. K., aged 32, had had five children, three years elapsing since the last pregnancy. Four months before she was seen by us she noted a lump in the breast and secretion at the nipple. Some pains were present over the lump. The discharge from the nipple was watery. The skin was markedly adherent to the tumor. The mass measured 6 by 4 by 4 cm. The peau d'orange appearance was present. A preoperative diagnosis of probable carcinoma was made, and mastectomy was performed.

"Remarkable atypical proliferation of lining cells of ducts which considerably resembles carcinoma but the cells are hydropic and degenerating. Many giant cells."

CASE 7.—A. T., aged 39 years, had had four pregnancies, three years elapsing since the last one. One year before she was seen by us she had pain in the left breast accompanied by redness. This disappeared in two weeks. Two weeks before she had a dull pain in this breast and found a lump present. There was a sinus near the nipple. The nipple was retracted. Marked skin adherence was present. The mass measured 5 by 6 by 3 cm. Enlarged nodes were present in both axillae. A roentgenogram of the chest was negative for tuberculosis or cancer. A peau d'orange appearance was present. A preoperative diagnosis was made of tuberculous mastitis (fig. 5), and mastectomy was performed.

"In this case the plasma cell exudate is limited to walls of ducts; the epithelial proliferation is very marked and at some points resembles comedocarcinoma. More often the proliferating epithelial cells degenerate into giant cells. Guinea-pig inoculation indicated."

Fig. 6 (case 8).—Photograph showing a mass in the right breast measuring 8 cm. in diameter. The nipple is retracted; the breast is elevated and irregular in outline; skin attachment is present. There is "a chain of hard axillary nodes extending across the axilla." It is a typical case of plasma cell mastitis.

CASE 8 (fig. 2).—C. M., aged 29, five months before she was seen by us had had a miscarriage. Following this there was caking of the breast. One month ago she noticed a lump which had been increasing in size. It was not tender. There was a discharge at the nipple. The breast was elevated and larger than the opposite breast. The nipple was retracted, and skin attachment was present. There was a mass measuring 8 by 8 by 8 cm. and some smaller lumps about this. A chain of large nodes extended from the tail of the breast across the axilla. A roentgenogram of the chest was negative. The diagnosis of carcinoma was made, and the patient was given a series of radium packs. Mastectomy was then performed.

"Main lesion surrounds and involves the large ducts which are filled with puriform material and epithelial detritus. There is a rich wide periductal infiltration of plasma cells, but no diffuse areas of infiltration. Many giant cells. Stain for tubercle bacillus negative."

CASE 9.—P. G., aged 31, had had three children, one and a half years elapsing since the last lactation. Three months before coming to us there were redness and tenderness in the breast, which subsided under cold applications, leaving a hard lump. There was no discharge at the nipple, which was markedly retracted. The tumor was adherent to the skin. The mass measured 8 by 6 by 6 cm. Several large axillary nodes and a peau d'orange appearance were present. A diagnosis was made of a very cellular, highly malignant carcinoma. The patient received a series of radium packs. Radical mastectomy was performed.

"Gross diagnosis suggestive of tuberculosis. The lesion consists of dilatation of many large and small ducts by puriform material containing many plasma cells and exfoliated epithelium; there are very few polynuclear leukocytes. About the ducts there is rather wide plasma cell infiltration. There are many giant cells of all sizes. Hyperplastic lymphadenitis."

CASE 10 (fig. 1).—F. S., aged 32, had had one child, five and a half years elapsing since the last pregnancy. Symptoms began with intermittent pain in the left breast which had been present for one year. There was no discharge from the nipple. The left breast was markedly heavier than the right. The nipple was retracted. A pig-skin appearance was present. There was a diffuse thickening throughout the outer half. One large hard node was present in the axilla. The breast was opaque to transillumination. Our diagnosis was plasma cell mastitis. The patient was urged for a period of two years to have this diagnosis confirmed by operation. At the end of this time she went to another hospital where a radical mastectomy was performed with the diagnosis of carcinoma. The slides were loaned to us, and Dr. Ewing, after examination, stated it was a typical case of plasma cell mastitis.

Bacteria.—The picture afforded by plasma cell mastitis frequently suggested that careful bacteriologic studies be carried out. Unfortunately, these studies were made in but four of our cases. In case 1 there was obtained "a pure growth of a large coccus, not identified." In another case there was "a rich growth of a large coccus growing in fours and pairs laterally dividing." In two cases the lesion so closely simulated tuberculosis that guinea-pig inoculations were carried out. Both cases proved negative for tuberculosis. Among other phases of the disease process is the interpretation of the presence of bacteria and the bearing on the etiologic factors discussed by Dr. Ewing.

Pathologic Interpretation (by Dr. James Ewing).—"From a survey of the present material it appears that we are applying the term plasma cell mastitis to a special group of cases which belong in the general class of chronic or subacute suppurative inflammation of the duct system of the breast. These cases differ from the ordinary suppurative mastitis in the absence of definite abscesses and generally in the wide extent of the process. The process is also much less acute and the productive element much more pronounced than in suppurative mastitis. These facts indicate that bacterial infection plays a less prominent rôle and chemical irritation a more prominent rôle than in suppurative mastitis. In the particular group of cases which has attracted our attention the plasma

cell infiltration is extremely abundant and widespread, producing rather bulky tumor masses which clinically resemble active carcinoma, and even under the microscope may be difficult to distinguish from cellular carcinoma.

"The main gross anatomic feature is the presence of many much thickened ducts, which are filled with puriform material, and may extend over a large segment or nearly the whole of the breast. In the most characteristic cases the cellular exudate is diffuse, making a broad opaque, sometimes, yellowish tumor-like mass, in which the distended ducts are less obvious or even not visible. These are the cases which resemble carcinoma, but as a rule, there are small foci of puriform softening which are not found in carcinoma.

"The plasma cell exudate begins in the walls of the ducts and extends between acini in adjoining lobules when the process becomes diffuse. Polymorphonuclear leukocytes are present in variable numbers, but are often quite scanty. The phagocytosis of fat is a prominent feature and many of the cases show a great many large plasma cells engorged with fat and resembling xanthoma. These areas have a yellow color.

"Proliferation of the lining epithelium is a peculiar and prominent feature. The affected ducts are lined by from six to ten rows of large somewhat hyperchromatic epithelial cells, which often raise the suspicion of carcinoma of the duct. Yet the later progress of these proliferating cells ends not in carcinoma but in generation fragmentation and formation of giant cells of all sizes. Many of the giant cells and degenerating epithelium produce structures which closely resemble tuberculosis. Usually the foreign body nature of these giant cells is obvious because they usually contain much fat. Stains for tubercle bacilli are negative, and guinea-pig inoculations are also negative. The appearance of the proliferating epithelium in the early or milder stages of some cases strongly recalls the appearance of comedocarcinoma. It seems probable that comedocarcinoma arises under much the same conditions, but only when the chemical irritation is more prolonged and less severe. In a few cases the proliferating epithelial cells produce many small slightly hyperchromatic giant cells, a picture which again approaches that of large cell carcinoma.

"Bacteria have been isolated from several cases, but the exact identity of the strains have not been determined nor their exact relation to the inflammatory process. Usually the bacteria are large cocci growing in pairs or short chains. They are never very numerous, and some cultures are negative. It may therefore be concluded that while bacterial infection is probably a necessary factor in the process, its influence is less prominent than the chemical effect of decomposing fatty material."

SUMMARY

A study is made of a lesion of the breast which we term plasma cell mastitis. Ten cases are analyzed. This lesion is difficult to distinguish from mammary cancer by clinical signs alone. The signs of cancer are present, such as hardness of the tumor, retraction of the nipple, skin attachment, peau d'orange appearance and axillary nodes. With such signs present, the only possibility of arriving at a correct diagnosis lies in the evaluation of the characteristic history. The typical history is that at some preceding date an inflammatory process was present in a nonlactating breast, which process was accompanied by redness, mild tenderness and mild discomfort. As the symptoms of the acute phase pass off, a residual hard mass remains. This mass is not tender or painful. In eight of our ten cases, mastectomy was performed because of the difficulty of diagnosis. The lesions had most of the signs of mammary carcinoma. The present analysis of our cases shows, however, that this is a diagnosable lesion clinically. The microscopic interpretation is very puzzling, as at times the lesion closely simulates comedocarcinoma and at other times tuberculous mastitis. It is a precancerous lesion and should be treated by local removal only.

SURGICAL ATTEMPTS AT INCREASING SUGAR TOLERANCE

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AND
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CHICAGO

An attempt to increase the utilization of carbohydrates by surgical means may follow various courses. It may try to stimulate the formation of islets in the pancreas and increase the insulin output of the gland. If one regards the insulin deficiency as the primary cause of diabetes, an increase of insulin production would be highly desirable. Minkovski's [1] belief that the diabetic organism is unable to utilize carbohydrate has been greatly strengthened by the isolation of insulin, and seemingly gave the final blow to the alternate theory of diabetes, emphatically upheld by von Noorden [2] since 1910, namely, that hyperglycemia and glycosuria are due to an overproduction of sugar, owing to a hyperirritability of the sugar-producing apparatus in the liver. This theory naturally emphasizes the nervous regulation of carbohydrate metabolism and would call for an attack on the nerve supply of organs that are effecting the utilization of carbohydrates. Our surgical attempts were shaped to conform to both theories, and we are presenting a summary of our efforts in both directions.

METHODS OF STUDY

In previous communications [3] we have described various trials with oral, intraperitoneal and intravenous administration of dextrose to determine sugar tolerance.

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Aided by a grant from the Billings Club. The more recent work on celiac ganglionectomy was aided by a grant of the Committee on Scientific Research of the American Medical Association.

1. Minkovski, O.: Untersuchungen über den Diabetes mellitus nach Exstirpation des Pankreas, Arch. f. exper. Path. u. Pharmakol. **31**:85, 1893.

2. von Noorden, C., and Isaac, S.: Die Zuckerkrankheit und ihre Behandlung, ed. 8, Berlin, Julius Springer, 1927, p. 216.

3. de Takáts, G.: Correlations of External and Internal Pancreatic Secretion: I. General Considerations and Review of the Literature, Arch. Surg. **19**:771 (Nov.) 1929; II. The Histologic Changes in the Isolated Tail of the Pancreas, ibid. **19**:775 (Nov.) 1929. de Takáts, G., and Nathanson, I. T.: III. The Effect

By far the most accurate and constant data were obtained with the method of Woodyatt, Sansum and Wilder,[4] who used an electric pump to administer sugar solutions at timed rates. All dogs were on a standard kennel diet and were completely relaxed, in a basal state, during which a continuous injection of 5 per cent dextrose was given for one hour. Excitable dogs or dogs that were difficult to train to lie quietly for an hour were rejected. The autoclaved, 5 per cent solution of Pfanstiehl dextrose was passed through a waterbath with a glass coil, so that the temperature of the solution was even throughout the experiment. Urine was then collected for twenty-four hours, and the sugar, if present, was determined by Benedict's method. From two to three preoperative determinations were made. The normal dog, completely relaxed, shows a sugar tolerance of from 1.6 to 1.8 Gm. of dextrose per kilogram per hour, but most dogs, after several determinations, may show a tolerance of from 1.8 to 1.9 Gm. per kilogram of body weight, which amount, if injected intravenously for an hour, will fail to produce a glycosuria. In many of the later experiments, blood sugar determinations were also made at the beginning and at the end of the injection, and were followed up to four hours after the completion of the test, to see how fast the excess of sugar would disappear from the blood stream. It will be noted that our figures for normal tolerance are much higher than those of the originators of the method, which is probably due to the use of isotonic solutions in our work and the insistence on complete relaxation of the animal.

Following various surgical procedures, which were to be tested, such tolerance determinations were repeated once or twice a month, the first determination usually being made two weeks after the operation. All dogs used in this series were observed for at least six months, but some were followed for over two years.

In addition, blood sugar curves were determined following small intravenous injections of epinephrine and insulin before and after the operation. Epinephrine was given in doses of 0.02 mg. per kilogram of weight, and insulin in doses of 0.1 unit per kilogram. The blood sugar was determined at ten, twenty and thirty minutes and one, one and a half and two hours after injection by the modified Folin-Wu method.

The operations performed were: (1) ligation of the tail of the pancreas, which was effected by tying a strong silk ligature or narrow tape of linen around the splenic portion of the gland; (2) adrenal denervation, which was obtained by cutting the splanchnic nerves and small sympathetic branches to the left adrenal gland and removing the right adrenal gland; (3) denervation of the liver, which was obtained by the complete severance of all structures in the liver pedicle with the exception of the hepatic artery, hepatic vein, hepatic duct and portal vein, which were carefully stripped and, in addition, touched with phenol, and (4) celiac ganglionectomy. The left adrenal gland was exposed by an incision running parallel to the left costal margin. The left suprarenal plexus was picked up and followed toward the median line. Above the celiac axis, the left and right semilunar ganglions were exposed and removed, their connections with subordinate plexuses being cut.

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of Ligation of the Tail of the Pancreas on Diastase in the Blood, ibid. **19**:788 (Nov.) 1929. de Takáts, G.; Hennett, F.; Henderson, D., and Seitz, I. J.: IV. The Effect of Isolation of Tail of Pancreas on Carbohydrate Metabolism, ibid. **20**:866 (May) 1930.

4. Woodyatt, R. T.; Sansum, W. D., and Wilder, Russell M.: Prolonged and Accurately Timed Intravenous Injections of Sugar, J. A. M. A. **65**:2067 (Dec. 11) 1915.

RESULTS OF OPERATIONS

Ligation of the Tail of the Pancreas.—In previous communications the suggestion of Mansfeld,[5] that a ligature around the body of the pancreas increases sugar tolerance, was investigated. There is adequate evidence to show that when the tail of the pancreas, which contains more islet tissue than the rest of the gland, is turned into a ductless gland by obstructing the external secretion, hypertrophy and hyperplasia of islet tissue develop in the ligated tail, with a corresponding increase in sugar tolerance. Observations on two diabetic children, on whom such an operation was carried out, confirmed the experimental findings of a rise in tolerance.[6]

It has been assumed by Mansfeld and other workers, who repeated his experiments,[5] that the increase in tolerance was due to a hyperfunction of islets in the tail of the pancreas. While this was unmistakably so a few months after the operation, biopsies undertaken from ten to fifteen months after the operation showed that the excluded portion of the pancreas had almost disappeared, with the exception of the duct and strips of sclerotic tissue around it (fig. 1). This is not surprising in view of the observation made on pancreatic transplants by Ivy and Farrell,[7] that an atrophy and fibrosis of the transplant took place when it was prevented from secreting pancreatic juice. The degree of sclerosis following obstruction of the duct has been carefully studied by Jorns,[8] who stated that a ligature of the duct would be followed by a greater rise in tolerance than a complete severance of the duct, because in the former case the duct would become reestablished and prevent the progressive strangulation of the islets.

In marked contrast to the atrophy of the part distal to the ligature, the unligated part of the pancreas seemed unusually bulky. A section taken from the same dog's pancreas, in which a marked fibrosis was present, distal to the ligature, showed an abundance of islet tissue proximal to the ligature (fig. 2). This compensatory hypertrophy was found in all five dogs that had a ligation of the pancreatic tail from eight to fourteen months previous to exploration. The regenerative power of

5. Mansfeld, G.: Versuche zu einer operativen Behandlung des Diabetes, Klin. Wchnschr. **6**:1, 1927.

6. (*a*) de Takáts, G., and Wilder, R. M.: Isolation of Tail of Pancreas in a Diabetic Child, J. A. M. A. **93**:606 (Aug. 24) 1929. (*b*) de Takáts, G.: Ligation of the Tail of the Pancreas in Juvenile Diabetes, Endocrinology **14**:255, 1930; The Effect of Ligating the Tail of the Pancreas in Juvenile Diabetes, Surg., Gynec. & Obst. **53**:45 (July) 1931.

7. Ivy, A. C., and Farrell, J. I.: A Method for the Subcutaneous Transplantation of the Tail of the Pancreas, Am. J. Physiol. **77**:474 (July) 1926.

8. Jorns, G.: Experimentelle und klinische Beiträge zur Pathologie der Langerhans'schen Inseln, Beitr. z. klin. Chir. **146**:1, 1929.

the pancreas has been emphasized by F. M. Allen,[9] Fahr [10] and others. Removal of pancreatic tissue, however, results not only in regeneration but in a superregeneration, as manifested by an increase in sugar tolerance [11] unless the gradual removal is carried to a point of exhaustion in the remnant.

When the ligated portion of the pancreas is removed from the dog, which shows an increase in sugar tolerance, the tolerance does not drop, but on the contrary rises (fig. 3). This can be explained only by the stimulating effect of the removal of the tail on the remnant. Thus, we were unable to confirm the statement of Mansfeld,[5] that the removal of

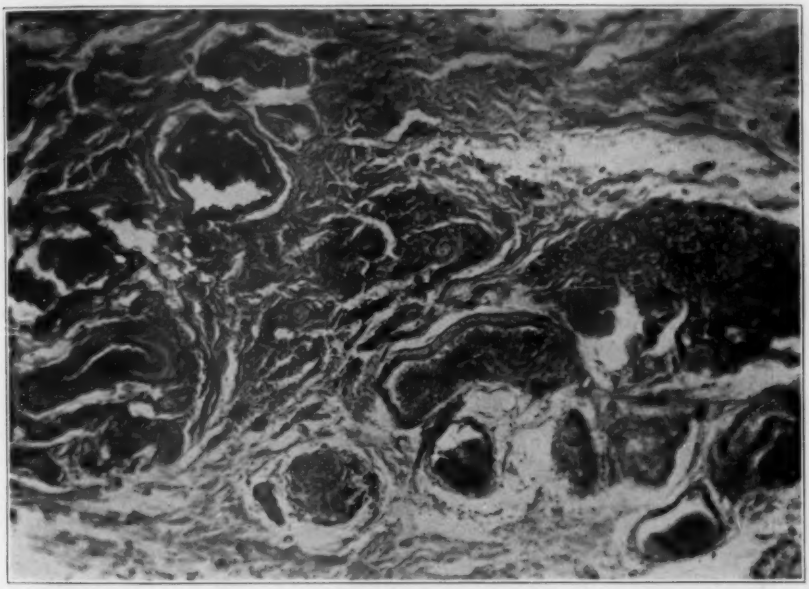

Fig. 1.—Marked sclerosis of the ligated tail of the pancreas, one year after the operation. There are only small patches of parenchyma left. The blood vessels are numerous and have thick walls, indicating the increased resistance of the tissues to blood flow. There are no islets visible in this field. Fibrous connective tissue dominates the picture.

the ligated tail of the pancreas terminates the increased tolerance in the experimental animal.

The rise in tolerance then observed following a massive ligature around the body of the pancreas produces a hypertrophy and hyperplasia

9. Allen, F. M.: Studies Concerning Diabetes and Glycosuria, Boston, W. M. Leonard, 1913.

10. Fahr, T.: Diabetes Studien, Virchows Arch. f. path. Anat. **215**:247, 1914.

11. Elias, M., and Waller, K.: Zur Wiederherstellung der Funktion des Inselapparates, Ztschr. f. d. ges. exper. Med. **74**:81, 1930.

of the islets in the ligated portion; later, however, a progressive sclerosis replaces the destroyed acinar tissue and invades the islands, and a compensatory regeneration and even a hyperregeneration of the unligated portion supervene. As the insular tissue functions according to existing needs, a hyperfunction cannot be expected to persist in the normal animal.[3]

The experience with two diabetic children, in whom the ligation of the tail of the pancreas was performed, indicated an unmistakable improvement of sugar tolerance, but as long as further hypodermic administration of insulin was still necessary the operation did not accomplish its object.

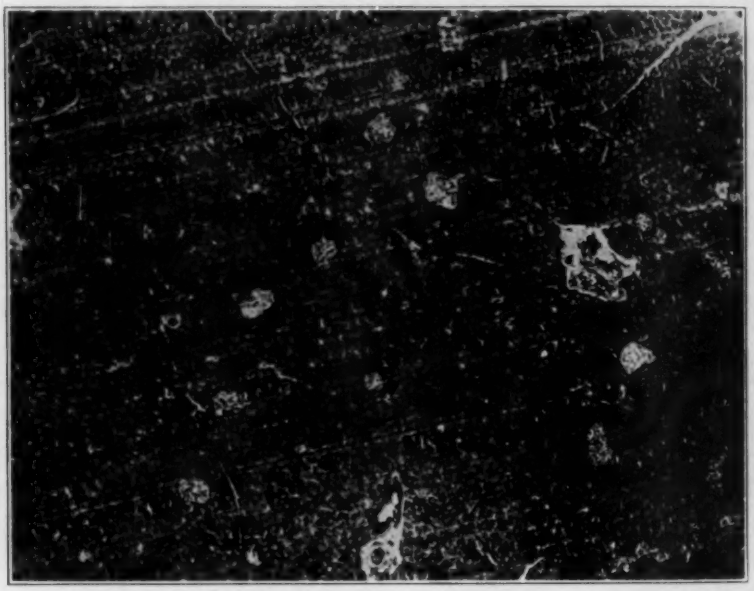

Fig. 2.—Section from the body of the pancreas. The tail was ligated six months previously. There is an abundance of islet tissue. The section looks like many of the pictures obtained from ligated portions, but there is no dilatation of ducts and no increase in fibrous tissue.

Ligation of the Tail of the Pancreas and Adrenal Denervation.—It was reasonable to assume that if an increased or uninhibited secretion of insulin were present following ligation of the tail of the pancreas, the mechanism which normally maintains the blood sugar level would attempt a compensation. The emergency theory of Cannon, McIver and Bliss [12] could be well applied to a prolonged state of hyperinsulinism.

12. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: A Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, Am. J. Physiol. **69**:46, 1924.

Thus, Riddle [13] in doves and Langecker [14] in rabbits produced an increase in the size and weight of the adrenals following prolonged administration of insulin. In man, Gray and Feemster [15] described a hypertrophy of the suprarenal medulla in the presence of insular hypertrophy and hyperplasia, whereas Chiari [16] reported an insulin-resistant diabetes with a large suprarenal hyperplasia. The patient had received 100 units of insulin without any lowering of blood sugar.

That such a suprarenal response might be at play following the increased activity of islet tissue after ligation of the pancreatic tail was suggested to us by an unmistakable enlargement of the adrenals seen in four of six dogs that came to autopsy not earlier than a year after the

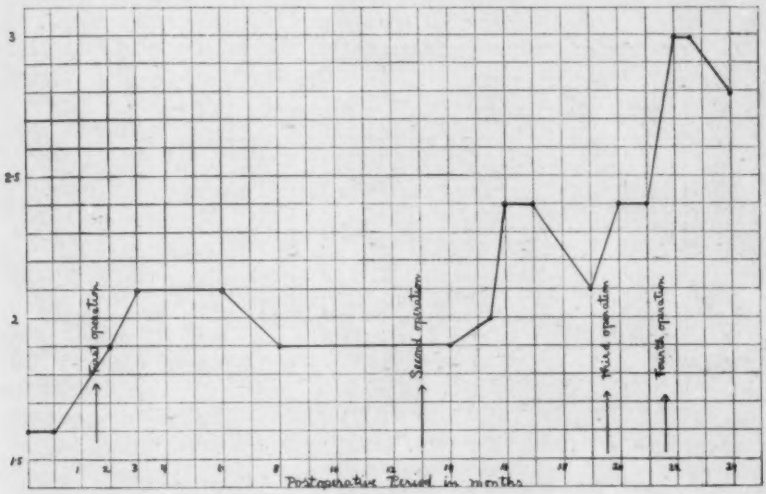

Fig. 3.—Sugar tolerance curve of dog 50 (measured in grams per kilogram per hour). Following ligation of the tail of the pancreas (on March 20, 1930), the tolerance rose from 1.6 Gm. per kilogram per hour to 1.9 Gm., and after three months, to 2.1 Gm. This tolerance was maintained for three months, after which a decline took place. The removal of the ligated tail (on April 23, 1931) did not decrease the tolerance further, but, on the contrary, a second rise took place, reaching the peak of 2.4 Gm. three months after the second operation. When this curve declined, splanchnic section on one side (on September 29) and later on the other side (on November 24) resulted in a steep rise of tolerance, becoming stabilized at 2.8 Gm.

13. Riddle, O.; Honeywell, H. E., and Fisher, W. S.: Suprarenal Enlargement Under Heavy Dosage of Insulin, Am. J. Physiol. **68**:461 (May) 1924.

14. Langecker, Hedwig: Der Einfluss chronischer Insulinzufuhr auf die Nebennieren beim Kaninchen, Arch. f. exper. Path. u. Pharmakol. **134**:155, 1928.

15. Gray, S. H., and Feemster, L. C.: Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born of a Diabetic Mother, Arch. Path. **1**:348 (March) 1926.

16. Chiari, H.: Ein Fall von Diabetes mit Hypertrophie der Nebennierenrinde, Wien. klin. Wchnschr. **42**:1318 (Oct. 10) 1929.

tail of the pancreas was isolated. In three cases the medulla was cystic and the cortex enlarged. When adrenal denervation was added to ligation of the pancreatic tail, the sugar tolerance rose up to the fourth month, closely corresponding with the rise following the pancreatic operation, but instead of declining after the fifth month, it continued to rise, reached a peak at the sixth month and remained high until the eighth month, the end of the observation (fig. 4). There was no enlargement of the adrenals in this series.

Thus, the second group of experiments seemed to inhibit the medulliadrenal response to the increased activity of the insular apparatus. But in the light of the experiments of Britton and his co-workers,[17] who found that cats became exceedingly sensitive to insulin following inac-

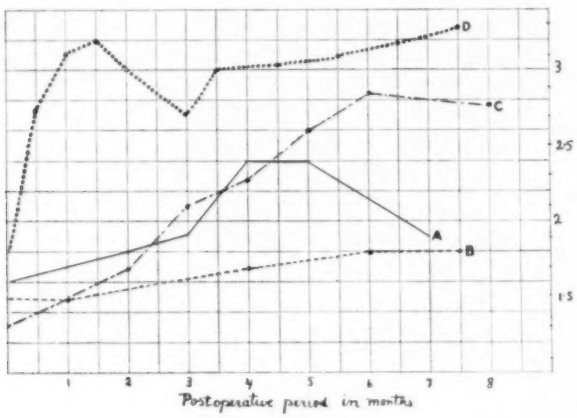

Fig. 4.—Composite graph, indicating the effect of various operations on sugar tolerance (measured in grams of dextrose per kilogram per hour). *A* represents the fluctuations in tolerance following ligation of the tail of the pancreas (in five dogs). A gradual rise, a peak at the fourth month, a decline after five months and a somewhat higher status at seven months than before operation are shown. *B* shows the tolerance after denervation of the liver (two experiments). There was no appreciable rise in tolerance, except that due to a better relaxation of the animal. The tolerance never rose above 2 Gm. per kilogram per hour. These two experiments also serve as controls, to show that repeated intravenous determinations per se do not increase tolerance above the normal level. *C* represents the tolerance curves of five dogs with denervation of the adrenals and ligation of the tail of the pancreas. The rise in tolerance in these dogs showed a gradual character, but around the fifth month, when tolerance declined again in a dog with ligation of the tail alone, the five animals increased their tolerance to almost 3 Gm. per kilogram per hour. *D* illustrates the average of the tolerance curves of five dogs that had undergone celiac ganglionectomy. With the exception of one dog in which the tolerance had not been determined before the fifth month, the tolerance rose suddenly after the operation, in one case reaching the height of 3.8 Gm. per kilogram per hour.

17. Britton, S. W.; Geiling, E. M. K., and Calvery, H. O.: Medulli-Adrenal Secretion and Carbohydrate Metabolism, Am. J. Physiol. **84**:141, 1928.

tivation of the adrenal medulla, adrenal denervation per se must profoundly influence carbohydrate metabolism. Thus the blood sugar curves following the administration of epinephrine and insulin show a sluggish response to the former and a marked hypersensitivity to the latter (fig. 5). In one instance adrenal denervation was claimed to protect a pancreatectomized dog from diabetes.[18]

Denervation of the Liver.—This operation was undertaken with the idea of interrupting all nervous impulses that might lead to a mobilization of glycogen. In 1894, Cavazzani [19] observed that the liver cells lost glycogen and became smaller, and that the blood sugar rose, when the celiac plexus was stimulated with an electric current. Recently, Depisch, Hasenöhrl and Schönbauer [20] reported a flattening of tolerance curves following denervation of the liver pedicle both in normal and in partially pancreatectomized dogs. Soon after we started this series of experiments, Donald's work from Mann's laboratories appeared, which

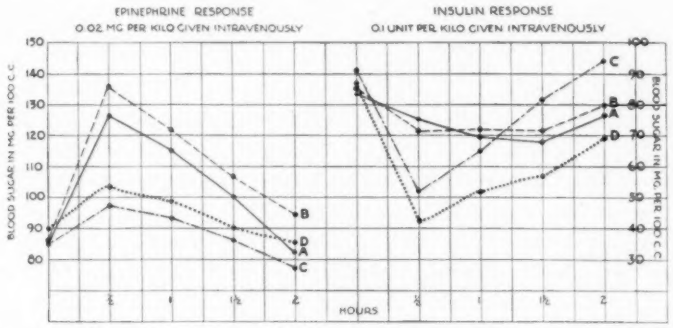

Fig. 5.—Response to epinephrine and insulin following various surgical procedures. Epinephrine was given in doses of 0.02 mg. per kilogram of body weight in 10 cc. of physiologic solution of sodium chloride, intravenously. Insulin was administered intravenously, 0.1 unit per kilogram of body weight. *A* is the average of thirty curves of normal controls. In *B* (average of five curves), note that denervation of the liver did not change the response to epinephrine or insulin. Epinephrine hyperglycemia was diminished in the group that underwent ligation of the pancreatic tail and adrenal denervation (*C*, average of thirty curves). The most striking change in the response to insulin occurred in the dogs with denervated adrenals (*D*, average of ten curves), because not only was the hypoglycemic dip marked but the recovery to a normal level was retarded. The dogs with denervation of the liver behaved like the control animals.

18. Ciminata, H.: Einfluss der Durchschneidung der Nebennieren auf den Diabetes mellitus, Klin. Wchnschr. **11**:150, 1932.

19. Cavazzani, Emil: Ueber die Veränderungen der Leberzellen während der Reizung des Plexus coeliacus, Arch. f. d. ges. Physiol. **57**:181, 1894.

20. Depisch, F.; Hasenöhrl, R., and Schönbauer, L.: Die Durchschneidung der vegetativen Nerven im Ligamentum hepatoduodenale, Klin. Wchnschr. **9**:1437, 1930.

shows conclusively that denervation of the liver does not affect carbohydrate metabolism.[21] Therefore, we contented ourselves with the study of two dogs that had been observed for over seven months and that showed identical results, namely, that denervation of the liver pedicle did not increase sugar tolerance (fig. 4). We have used these two dogs for controls, illustrating that repeated tolerance determinations will not increase the sugar tolerance, at any time, over 2 Gm. of dextrose per kilogram per hour. The response to epinephrine and insulin does not differ from that of the controls (fig. 5).

Celiac Ganglionectomy.—This operation denervates extrinsically the pancreas, the adrenals and the liver. The latter receives some vagal branches from the left side, which may be sectioned separately. The nervous control of carbohydrate metabolism has been emphasized in Claude Bernard's experiments with piqûre. The older literature has been summarized by Mock and one of us (Dr. de Takáts.[22]). The reviews of Pollack [23] and McLeod,[24] together with several experimental studies,[25] indicate (1) that vagal stimulation produces hypoglycemia, presumably through secretion of insulin, and (2) that splanchnic section increases the sensitivity to insulin. The exaggerated response of sympathectomized animals to insulin has recently been investigated by Dworkin.[26]

In the light of these data it seemed important to examine the effect of celiac ganglionectomy on sugar tolerance, as previous data in the literature were absent. The operation was performed on five dogs, and the results were followed over a period of at least seven months (fig. 4). The rise in tolerance has been higher than that observed with any other procedure, in one dog reaching the peak of 3.83 Gm. per kilogram per hour. This change took place immediately after the operation, when

21. Donald, Joseph M.: Studies on Carbohydrate Metabolism of the Liver, Am. J. Physiol. **98**:605 (Nov.) 1931.

22. Mock, Harry E., and de Takáts, G.: Hyperglycemia Following Head Injuries, Ann. Surg. **90**:190 (Aug.) 1929.

23. Pollack, Leo: Pathologie und Physiologie der Blutzuckerregulation, Ergebn. d. inn. Med. u. Kinderh. **23**:337, 1923.

24. McLeod, J. J. R.: Regulation of the Secretion of Insulin, Lancet **2**:512, 1931.

25. Rupp, W.: Ueber den Einfluss des Nervensystems auf den Zuckergehalt des Blutes, Ztschr. f. d. ges. exper. Med. **44**:476, 1925. Britton, S. W.: The Nervous Control of Insulin Secretion, Am. J. Physiol. **74**:291, 1925. Clark, G. A.: The Influence of the Vagus on the Islets of Langerhans, J. Physiol. **59**:466, 1925. Geiger, E., and Szirtes, F.: Maximale Hypoglykemie ohne Insulin, Arch. f. exper. Path. u. Pharmakol. **119**:1, 1927. Dresel, K., and Omonsky, F.: Der Einfluss des Vagus- und der Splanchnicusdurchschneidung auf die Adrenalinhyper- und die Insulinhypoglykämie, Ztschr. f. d. ges. exper. Med. **53**:371, 1927.

26. Dworkin, S.: The Response of Sympathectomized Animals to Insulin, Am. J. Physiol. **98**:461 (Oct.) 1931.

the dogs had sufficiently recovered. The tolerance does not fall, but on the contrary seems to rise slowly (fig. 4). The response to insulin is markedly exaggerated (fig. 6). When the blood sugar is determined at the completion of the intravenous injection and followed for several hours afterward, the low peak at the completion of injection and the hypoglycemic level at one hour are striking in the ganglionectomized dog (fig. 7).

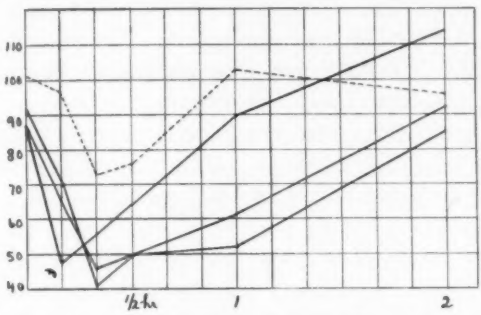

Fig. 6.—Response to insulin following celiac ganglionectomy. The normal, preoperative response is indicated by the interrupted line. The straight lines indicate the response to insulin in three dogs following operation. Note the maximal dip in from ten to twenty minutes, which reached the value of 41 mg. of dextrose following the intravenous administration of 0.1 unit of insulin per kilogram of body weight. The blood sugar is measured in milligrams per hundred cubic centimeters.

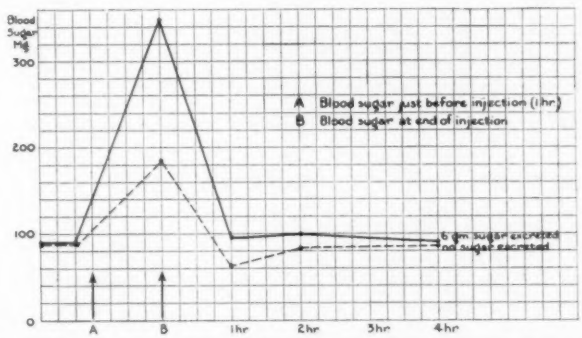

Fig. 7.—Blood sugar determinations before, at the completion of, and for several hours following, the intravenous administration of 5 per cent dextrose at the rate of 2 Gm. per kilogram per hour. The straight lines indicate the normal control (a dog, weighing 17 Kg.); the interrupted line, a dog weighing 20 Kg., in which the celiac ganglion was removed five months previously.

The dogs in all four series maintained excellent health and did not lose weight. Their tolerance was occasionally influenced by skin or respiratory infections. In only one dog in the last series did diarrhea and a progressive loss of weight develop. He was excluded from further observation.

COMMENT

It seems, then, from the foregoing data that sugar tolerance in the normal dog, as determined with intravenous injections of dextrose at timed rates, may be raised by various surgical procedures. The rise in tolerance that follows the ligation of the tail of the pancreas comes on gradually, reaches its peak from the third to the sixth month following operation and later declines. The atrophy of the ligated tail produces a superregeneration of the unligated portion which may be accentuated by a secondary removal of the ligated part. Like all processes of repair, the superregeneration does not progress or remain unchanged, but gradually adapts itself to the functional needs of the normal body. Our observations on diabetic children with this method would not indicate, outside of a decided increase in tolerance, that the original diabetogenic factor had been excluded. This was pointed out in our first communication with Wilder.[6a]

If, however, the point of attack is the nervous regulation of carbohydrate metabolism, the most rapid and greatest increase in tolerance is accomplished by celiac ganglionectomy. The tolerance rises rapidly and is maintained at the average level of 3.4 Gm. per kilogram at the eighth month, although an individual rise of 3.8 Gm. has been recorded, and one dog showed a tolerance of 3.6 Gm. at the end of one year. This means that a dog weighing 15 Kg. would utilize, instead of 30 Gm. of dextrose given intravenously, an amount of 51 Gm., a hitherto unobserved rise in tolerance.

The explanation of this large rise in tolerance cannot yet be attempted. As denervation of the liver has no effect on sugar tolerance, there remains the effect of denervation on the pancreas and adrenals. That the inactivation of the adrenals increases insulin susceptibility has been shown without doubt, and our own observations confirm this. As to the effect of celiac ganglionectomy on the pancreas, an increased flow of blood or an inhibition of vasoconstrictor impulses to the vascular system of the islets could be thought of. This operation also inhibits the enzyme secretion of the pancreas.[27] If it could be shown that the rise in tolerance is not entirely lost in the absence of the pancreas, this would focus the entire problem on the adrenals.

If these experiments on the nervous control of carbohydrate metabolism are to have a clinical application, they would have to be based on the acceptance of the "overproduction" theory of diabetes, with a denial of impairment in carbohydrate oxydation by the diabetic organism. The work of Soskin [28] has furnished significant data in this direction.

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27. Baxter, S. G.: Nervous Control of the Pancreatic Secretion of the Rabbit, Am. J. Physiol. **96**:349, 1931.

28. Soskin, S.: The Utilization of Carbohydrate by Totally Depancreatinized Dogs Receiving No Insulin, J. Nutrition **3**:99 (Sept.) 1930.

SUMMARY

Four series of experiments have been conducted with the object of increasing sugar tolerance in the normal dog: (1) ligation of the tail of the pancreas, (2) ligation of the tail of the pancreas with denervation of the adrenals, (3) denervation of the liver and (4) celiac ganglionectomy. The first procedure laid stress on an increased or uninhibited output of insulin, which does not persist in the normal animal indefinitely. When adrenal denervation is added, however, to the first operation, the tolerance is maintained on a high level. Denervation of the liver did not affect sugar tolerance. Celiac ganglionectomy raised the sugar tolerance to hitherto unobserved levels, and its effect has lasted as long as fourteen months unchanged.

Tests for epinephrine and insulin susceptibility showed that liver denervation did not alter the normal response to either of these hormones. However, adrenal denervation and celiac ganglionectomy flattened the epinephrine-glycemia curves and markedly increased the insulin hypoglycemia. These tests indicate the profound influence of these operations on carbohydrate metabolism.

122 South Michigan Avenue.

ABSTRACT OF DISCUSSION

DR. JOSEPH A. DANNA, New Orleans: I have followed with considerable interest reports in the recent literature of surgical removal of adenomas and other tumors of the pancreas which were giving rise to clinical pictures suggestive of hyperinsulinism. The successful results in a number of these cases have helped to place the pancreas, or at least the island tissue of the pancreas, in the group of glands like the thyroid, pituitary, parathyroid, etc., in that it is capable of hyperfunction as well as hypofunction. The surgical results in a number of cases of hyperinsulinism have corresponded with the results obtained in thyroidectomy, operations on the pituitary and parathyroid glands, etc. We seemed to be quite helpless, however, in influencing the course of diabetes or hypo-insulinism by any surgical procedure.

The wonderful results following sympathectomy in Raynaud's disease, Buerger's disease and even angina pectoris are familiar to all of us. It remained for Dr. de Takáts, however, to conceive the possibility of attacking the organs concerned with sugar metabolism through the removal of their sympathetic control. The results which he reports are remarkable. It only remains now to see how well a human being will stand the removal of the semilunar ganglions. I was reminded by Dr. de Takáts' experiments in denervation of the adrenal gland of the work of Dr. George Crile, who, I believe, has done more denervations of suprarenals in human beings than any one else. I was anxious to know whether he noted the same changes in blood sugar and sugar tolerance as took place in Dr. de Takáts' animals. I had hoped that Dr. Crile would be here to relate his own experience in this regard, but when I found that he was not coming, I wired him and received from him this answer: "Adrenal denervation increases sugar tolerance and lowers blood sugar. In a limited number of cases of operations on diabetic patients they have been greatly improved and may prove to be cured."

This I interpret as fully corroborative of Dr. de Takáts' work. I have not had any experience in the removal of the great splanchnic ganglions in the human being. Their comparative surgical inaccessibility will probably not encourage many of us, especially in the presence of so serious a condition as diabetes, to make the attempt.

I have been wondering as to the feasibility of performing the Leriche operation on the splenic artery and on the gastroduodenal arteries, separating the pancreas from its bed and tucking a layer of omentum between it and its bed. This itself would be a formidable and difficult procedure, and the very free arterial and hence, probably, sympathetic anastomoses and the difficulty of entirely isolating the pancreas would not promise much hope of marked lasting results. I shall look to the near future with considerable interest for further developments in this fascinating field, and especially to the results of the activity and further investigation of Dr. de Takáts.

Dr. J. Shirley Sweeney, Dallas, Texas: This interesting paper contains many promising implications. Dr. de Takáts has demonstrated something by his research that we cannot explain. To the internists he has raised some controversial points.

When we stop to remember that the cause of diabetes mellitus is unknown, it is easy to understand why there may exist different theories as to the pathologic physiology of the disorder. Dr. de Takáts refers to the overproduction theory of diabetes mellitus, stating: "If these experiments on the nervous control of carbohydrate metabolism are to have a clinical application, they would have to be based on the acceptance of the overproduction theory of diabetes, with a denial of impairment in carbohydrate oxidation by the diabetic organism," and at this point he refers to the experiments of Soskin as furnishing significant data in this direction. I wish that he would make this statement a little clearer. I think that in some of Soskin's depancreatized dogs there was evidence of active sugar metabolism as well as fat metabolism. Furthermore, I have always felt that fat metabolism was dependent on sugar metabolism. If the continued metabolism of sugar and fat might be ascribed to extrapancreatic insulin, the paradox might be explained, but since Best and his co-workers have recently proved there is no insulin except in the pancreas, we are in doubt again.

It is difficult for me to give up the idea that a deficiency of insulin is the reason for diabetes. It seems to me so much more physiologic than the concept of gluconeogenesis—a hypothetic process. Conversely, certainly when excessive insulin is produced, as in metastastizing carcinoma of islet tissue, we have the antithesis of diabetes mellitus. But neither time nor an audience, composed largely of surgeons, permits a technical discussion of this phase of the subject. In the ligation operation, nervous control was undisturbed and an increase in sugar tolerance resulted, presumably owing to a regeneration of islet structures or more insulin. This seemed to be true also in the cases in human beings described by Dr. de Takáts in other communications. True, the tolerance increased more following celiac ganglionectomy, but why is it not the same process, possibly by either blocking an inhibiting influence or by increasing pancreatic blood supply or diminishing adrenal secretion—a neutralizing substance?

The recent observations of Zimmerman and Soskin are noteworthy. They found that by ligating the parotid ducts of normal dogs they were able to increase sugar tolerance, whereas in depancreatized dogs the same operation produced no results.

There is an inextricable relation between sugar and fat metabolism. This is noted, especially in diabetes mellitus in adults, by the almost invariable antecedent obesity. Something, it seems, happens to fat metabolism and then to sugar metab-

olism. I have long had a lingering idea that there is another pancreatic hormone, possibly a different fraction, that controls fat metabolism, the disturbance of which precedes the insulin deficiency.

But whatever fanciful theories are inspired by Dr. de Takáts' work, the fact remains that he has demonstrated that in normal dogs and in diabetic children, though to a much less degree, sugar tolerance can be increased. In the two diabetic children that underwent the ligation operation reported by Dr. de Takáts in another paper, it seems that the greatest benefit was a stabilization of tolerance. This is certainly desirable. What else may grow out of this work is speculative. Speaking for those internists interested in diabetes, suffice it to say that we are eagerly awaiting further developments in this stimulating and practical research.

Dr. Seale Harris, Birmingham, Ala.: While I am not a surgeon, I have become much interested in the surgery of the pancreas, particularly as related to the treatment of the severe cases of hyperinsulinism which cannot be controlled by dieting, because it opens up possibilities for relieving patients who otherwise would be doomed to death or to recurring convulsions.

Dr. de Takáts has done some interesting work on the pancreas. He produced hyperinsulinism in dogs experimentally by ligating the tail of the pancreas, thereby increasing permanently their carbohydrate tolerance. Diabetes is essentially a disease of the pancreas. Allen's theory, that it usually results from a previous pancreatitis, I think is well established. Allen describes it as the "burnt-out fire of a previous conflagration." Since diabetes hypo-insulinism is essentially a disease of the pancreas, Dr. de Takáts conceived the idea that ligating the tail of the pancreas of diabetic patients might result in a permanent increase in the activity of the islet cells. Collaborating with Wilder, he operated on two diabetic children of fixed and known carbohydrate tolerance and carefully adjusted the dosage of insulin. In one of these cases the carbohydrate tolerance was increased but not to the point that insulin could be dispensed with entirely. Dr. de Takáts does not claim that his operation has passed the experimental stage, but his work is a distinct contribution to the study of the islet cell function.

Denervation of the suprarenal glands to control or cure diabetes, it seems to me, is not as hopeful a procedure as some think. The physiologic function of suprarenal secretion is in mobilizing glycogen, and it is questionable whether or not it has any effect on the production of insulin. Denervation of the suprarenals will reduce blood sugar by its effect in decreasing the amount of glycogen that is mobilized and metabolized, but it cannot have any effect in curing diabetes.

Dr. de Takáts and other prominent surgeons have demonstrated that operations on the pancreas are not as serious as was formerly supposed. In the last few years, ten or twelve operations on the pancreas for hyperinsulinism have been performed by as many surgeons, without a death, and in six cases of removal of adenomas of the pancreas associated with recurring convulsive seizures due to hyperinsulinsm, the patients have been cured clinically, and dextrose tolerance tests prove that the insulogenic cells of the pancreas are functioning normally. In pancreatic surgery the cooperation of the surgeon and the internist is absolutely necessary. No operation for increasing or decreasing islet cell function should ever be undertaken without accurate blood sugar studies having been made and without a well directed effort at control by diet. No surgeon should attempt an operation on the pancreas without a thorough knowledge of pancreatic anatomy and pathology. In properly studied cases, in which the operation is performed by an experienced and skilful surgeon, who has associated with him a clinician qualified to care for the patient's diet, pancreatic surgery is probably as safe as operations on the gallbladder.

Dr. Géza de Takáts, Chicago: The effect of the removal of semilunar ganglions in the normal dog has been carefully studied. These dogs maintain perfect health. They do not gain or lose weight. Occasionally there is an increased peristalsis with a diarrhea for a number of weeks, which, however, always adjusts itself. So far as I know, studies of the effect of celiac ganglionectomy performed for other reasons in human subjects have not been made. I do know, however, of patients who have had the splanchnic nerves cut, and in such cases there is an increased peristalsis for a few weeks.

Suprarenal denervation, of course, can be accomplished not only by Dr. Crile's technic but by bilateral splanchnic section, which seems to me a simpler procedure.

Regarding the remark of Dr. Sweeney, Soskin reported on totally depancreatized dogs which still utilized carbohydrates. Therefore his work would confirm the old conception that in diabetes the primary disturbance is an overproduction of sugar and that the insulin deficiency is secondary, resulting from exhaustion of the islets.

So far as diabetes in human beings is concerned, these experiments do not and cannot settle the etiology of diabetes, but it would seem that diabetes is not a uniform disease, that persistent hyperglycemia and glycosuria are a symptom. There must be a true pancreatic diabetes following, for instance, an acute pancreatic necrosis. There may be, perhaps, a neurogenic diabetes, the existence of which is denied by many.

Regarding the operations on the two diabetic children that Dr. Harris referred to, both patients showed a very beneficial effect in that sugar tolerance was stabilized. However, I have felt from the beginning that all we accomplished was to raise their sugar tolerance, and that they are taking now less insulin and perhaps a little more carbohydrate. It is with this idea in mind that we have undertaken the study of the nervous regulation of carbohydrate metabolism with the ultimate hope of attacking certain types of diabetes from this angle.

CARDIAC INNERVATION

EXPERIMENTAL AND CLINICAL STUDIES

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The late Sir James Mackenzie is reputed to have said that discussions on angina pectoris are usually futile, as they simply consist of the replacement of one speculative hypothesis by another. This has been true both as to the etiology of the disease and as to the most logical surgical method of preventing the attacks. It is not within the scope of this paper to review the multitudinous theories which have been put forward to explain the cause of these painful crises; suffice it to say that by their very number Mackenzie's dictum has remained substantiated for many years. Recently, however, an increasing number of cardiologists have subscribed to the theory of Keefer and Resnik,[1] that most cases of angina pectoris can be accounted for on the basis of anoxemia of the myocardium. The experiments of Sutton and Lueth [2] have given strong support to this theory of the etiology of cardiac pain, as they have shown in dogs that interruption of the flow of blood in a coronary artery causes an immediate and unmistakable pain response.

As concerns the second point at issue, there has been no unanimity of opinion concerning the best operative approach to the problem. In the most up to date review of cardiac surgery, Cutler [3] stated that little is known with any certainty about the nerve pathways concerned in angina pectoris. The reason for this present uncertainty is due to the number of operations which have been advocated and to the fact that all have given good results in some cases and complete failures in others. The reader who wishes to familiarize himself with these different procedures is referred to the writings of Jonnesco,[4] Leriche,[5]

From the Surgical Services of the Massachusetts General Hospital.

1. Keefer, C. S., and Resnik, W. H.: Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium, Arch. Int. Med. **41**:769 (June) 1928.

2. Sutton, D. C., and Lueth, H. C.: Pain, Arch. Int. Med. **45**:827 (June) 1930.

3. Cutler, E. C.: The Present Status of Cardiac Surgery, Surg., Gynec. & Obst. **54**:274, 1932.

4. Jonnesco, T.: Traitement chirurgical de l'angine de poitrine par la résection du sympathique cervico-thoracique, Bull. Acad. de méd., Paris **84**:93, 1920.

5. Leriche, R., and Fontaine, R.: The Surgical Treatment of Angina Pectoris, Heart **3**:649, 1928.

Danielopolu,[6] Hofer,[7] Coffey and Brown,[8] Richardson and White[9] and many others. Reid and Andrus[10] have reviewed the older operative procedures, and Swetlow[11] and White[12] the newer statistics of paravertebral injections of alcohol. The results of all operative methods are summarized in table 1, which is made up of statistics from the literature compiled by Cutler[13] and Fontaine,[14] with the addition of the reports of operations performed in the Massachusetts General Hospital.

The results of a five year study of this problem have convinced one of us (Dr. White) that the underlying factor which accounts for the unsatisfactory results following the cervical operations is the failure to interrupt enough of the essential nerve connections of the heart. As in many past problems, the possibility of reproducing a condition in animals has helped in the clinical solution. Sutton and Lueth's[2] method of producing cardiac pain by occluding the flow of blood in a coronary

TABLE 1.—*Surgical Procedures in Angina Pectoris*

	Upper Cervical Sympathectomies			Complete Cervical Sympathectomies			Thoracic Sympathectomies
	Fontaine	Cutler*	M.G.H.†	Fontaine	Cutler*	M.G.H.†	M.G.H.†
Number of cases	37	53	8	37	27	2	4
Results:							
Good	66.6%	41.5%	37.5%	56.8%	52%	50%	100%
Improved	12.3%	35.8%	.....	10.8%	18.5%	....	.....
Failures	5.3%	11.2%	50%	8.1%	7.5%	....	.....
Uncertain	5.3%	4%	.....	5.4%	.....	....	.....
Deaths (within 4 days of operation)	10.5%	7.5%	12.5%	18.9%	22%	50%	0

* Cutler's figures for mortality have been corrected to include deaths occurring within the first four days after operation.
† Massachusetts General Hospital.

6. Danielopolu, D.: L'angine de poitrine et l'angine abdominale, Paris, Masson & Cie, 1927.

7. Hofer, G.: Zur Chirurgie des vegetativen Nervensystems bei Angina pectoris, Wien. med. Wchnschr. **75**:1781 and 2441, 1925.

8. Coffey, W. B., and Brown, P. K.: The Surgical Treatment of Angina Pectoris, Arch. Int. Med. **31**:200 (Feb.) 1923.

9. Richardson, E. P., and White, P. D.: Sympathectomy in the Treatment of Angina Pectoris, Am. J. M. Sc. **177**:161, 1929.

10. Reid, M. R., and Andrus, W. De W.: The Surgical Treatment of Angina Pectoris, Ann. Surg. **81**:591, 1925.

11. Swetlow, G. I.: Paravertebral Alcohol Block in Cardiac Pain, Heart **1**:393, 1926.

12. White, J. C.: Angina Pectoris: Relief of Pain by Paravertebral Alcohol Block of the Upper Dorsal Sympathetic Rami, Arch. Neurol. & Psychiat. **22**:302 (Aug.) 1929.

13. Cutler, E. C.: Summary of Experience Up to Date in the Surgical Treatment of Angina Pectoris, Am. J. M. Sc. **173**:613, 1927.

14. Fontaine, R.: Les résultats actuels du traitement chirurgical de l'angine de poitrine, Thèse de Strasbourg, 1925.

artery has enabled us to find out what operative procedures are necessary for complete interruption of all the cardiac pain tracts. A second experimental procedure of our own has given us further insight into the efferent motor pathways. We propose in this paper to give the results of these experiments and to correlate these findings with our operative experiences.

EXPERIMENTAL METHODS FOR DETERMINING THE CARDIAC PAIN PATHWAYS

The method described by Sutton and Lueth [2] has been used in these experiments for the production of cardiac pain. The animals used were large young dogs, weighing from 10 to 23 Kg. Operation was performed under ether anesthesia, which was administered by insufflation through a catheter inserted in the lower part of the trachea. This method maintained adequate ventilation and distention of the lungs in the presence of open pneumothorax. The fourth rib was resected from the sternum to the midaxillary line and the pleura opened. The pericardium was then drawn up and an incision, 1 inch (2.54 cm.) long, made in it. This gave a good exposure of the tip of the left auricle with the upper portion of the left ventricle and the left part of the right ventricle. The left coronary artery could be seen appearing from under the auricular appendage. It is at this point that it splits into its circumflex and descending branches. The descending branch running downward over the interventricular septum is easily accessible in its upper portion. A fine silk ligature threaded on a curved needle was passed just beneath the uppermost portion of the descending branch of the left coronary artery and its accompanying veins (fig. 1). This was brought out through a glass tube with a flange at its lower end. The pericardium was then tightly closed around the flanged end of the tube, and the wall of the chest sutured in several layers around it to obtain an air-tight closure. Following aspiration of air from the pleural cavity the tracheal catheter was withdrawn and the animal allowed to recover from ether.

These animals seemed to suffer from no shock, and recovered rapidly from their anesthesia. Within an hour to an hour and a half they were up and walking around the laboratory as though little had happened. This procedure was carried out on four control dogs and on seventeen others following varied types of neurosurgical operations to test the presence or absence of conduction of pain. When the cardiac pain fibers were uncut, traction on the ligature for a period of only a few seconds invariably produced a characteristic stiffening of the limbs, a marked increase in the rate and depth of respiration, and if maintained for over ten or fifteen seconds a definite restlessness on the part of the animal. During the tests the dogs were allowed to lie on a large table without any form of restraint. Traction on the thread occluding the coronary artery was never maintained to the point at which the animal showed signs of even moderately severe pain, but was discontinued as soon as the dog appeared to be uncomfortable enough to shift his position. When the pull was released, the animals immediately settled down again in perfectly comfortable attitudes and resumed their normal, regular respiration. Respiration was recorded in each case on a kymograph registering the respiratory movements by means of a small band around the thorax which pulled out a rubber membrane on a small tambour each time the animal inspired. This tambour was connected through rubber tubing with a second tambour recording each inspiration by a downward stroke on the smoked paper. The respiratory tracing appeared to be

the best graphic method of recording painful stimuli. In one case a blood pressure tracing was made as well, but failed to show striking changes when the coronary circulation was occluded.

For want of a better word to describe the characteristic reaction to coronary occlusion, the phenomena described will be referred to hereafter as evidence of cardiac pain. It is most important, however, to emphasize that none of these animals was ever permitted to suffer acutely.

OBSERVATION

1. *Control Observations.*—Four dogs were tested by this method, and three of their respiratory tracings are reproduced in figure 2.

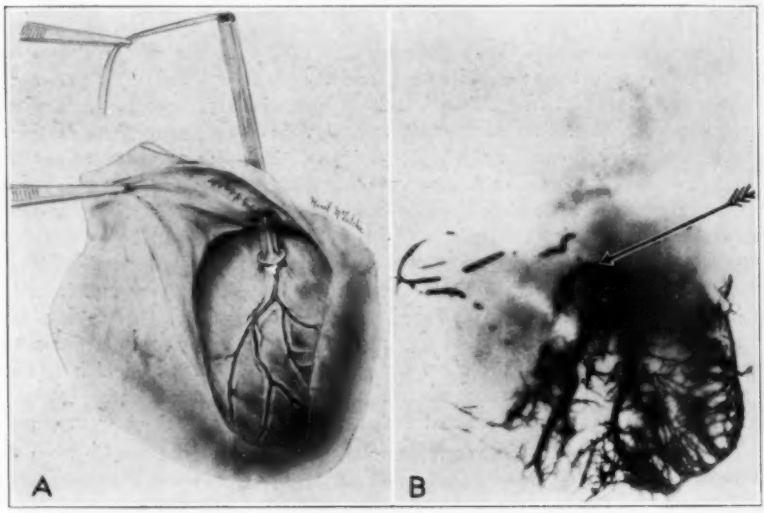

Fig. 1.—*A*, technic for temporary occlusion of descending branch of left coronary artery. *B*, roentgenogram after injection of metallic mercury at the point of constriction (arrow) in the left coronary artery shown in *A*. The blood supply of the entire anterior wall of the left ventricle, part of the right ventricle and the apex of the heart can be temporarily cut off by traction on the ligature.

These curves show strikingly the onset of deep, irregular respiration following occlusion of the descending branch of the left coronary artery. There is a striking contrast between this and the normal regular respiration seen before traction on the ligature and recurring a few seconds after its release. The behavior of these was equally striking and showed a characteristic change from a perfectly comfortable, relaxed animal to one with rapidly increasing discomfort. It was perfectly obvious that if the traction had been maintained a few seconds longer the dogs would have been suffering as acutely as persons in typical attacks of angina pectoris. The straightening and stiffening of the forelegs and

body were also suggestive of a person in an abrupt attack of angina pectoris or coronary occlusion. In each case the attack passed off within a few seconds of the release of tension on the ligature, and the dog again appeared to be perfectly comfortable and ready to rest quietly on the table.

2. *Effect of Left Stellate Ganglionectomy.*—Figure 3 shows the anatomic relationships between the vagus and sympathetic trunks in the dog. In the neck, just below the superior cervical sympathetic ganglion, these two structures combine and form a common vagosympathetic trunk. In the region of the middle cervical sympathetic ganglion the sympathetic again leaves the vagus nerve and passes as the annulus of Vieussens in front of and behind the subclavian artery. These two branches then unite to form the cervicodorsal or stellate ganglion, which in the

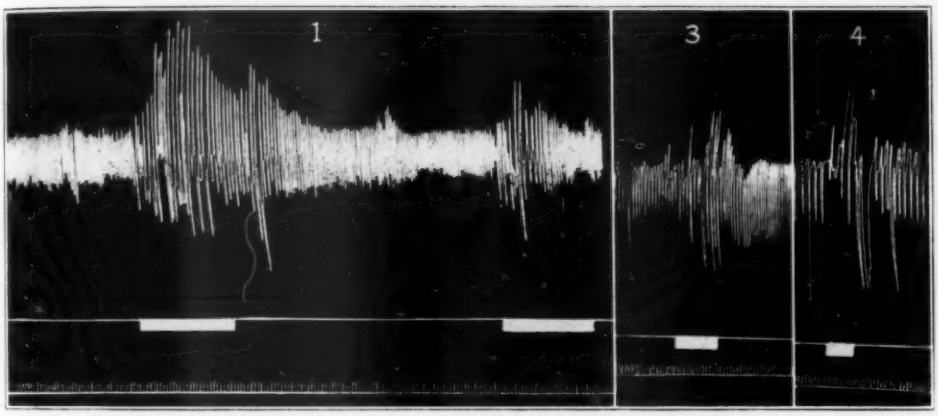

Fig. 2.—Respiratory movements in control dogs, showing response to periods of coronary occlusion of from ten to thirty seconds' duration. In this and each of the subsequent figures, the time intervals are marked in seconds and the duration of coronary occlusion by the broad white signal line.

dog is a fusion of the inferior cervical and first thoracic sympathetic ganglions. It is a large and most important structure, the origin of the inferior cardiac nerve and the first ganglion to receive a white communicant ramus, which means that it is the highest that is connected directly with the spinal cord. The superior and middle cervical sympathetic ganglions, on the other hand, are connected to the spinal cord only by nerve fibers which pass through the stellate ganglion. Below this ganglion the sympathetic trunk becomes considerably smaller. The lower ganglions correspond with each of the intercostal nerves and are connected to them by both white and gray rami.

While the classic sympathetic peripheral pathways run from the cervical and stellate ganglions to the heart, it is possible to see fine

postganglionic fibers leaving the upper two to four thoracic ganglions and running in the direction of the cardiac and pulmonary plexuses. Jonnesco and Enarchesco,[15] Braeucker [16] and Kuntz and Morehouse [17] have recently traced these fibers into the posterior cardiac plexus. Do these fibers carry important pain or motor stimuli which play an important part in angina pectoris? If so, it is obvious that in the human

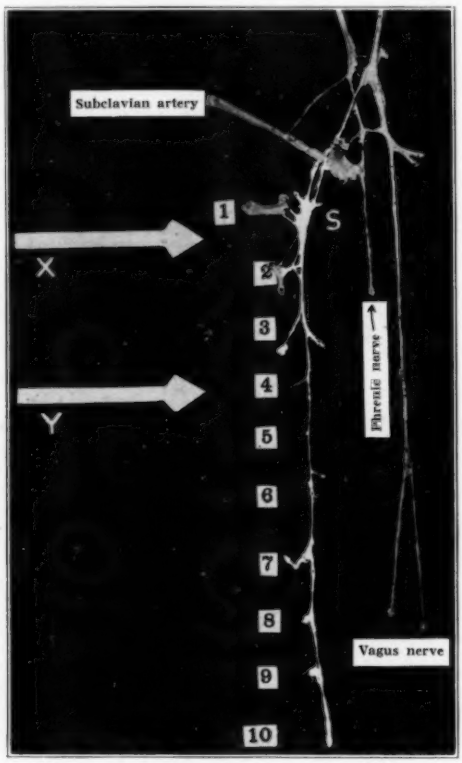

Fig. 3.—Photograph showing the thoracic sympathetic ganglions, the combined vagosympathetic trunk and the thoracic portion of the vagus nerve in the dog. The cervicothoracic or stellate ganglion is marked *S*. The other ganglions are numbered. When the sympathetic trunk is resected between the subclavian artery and the point *X*, cardiac pain is not interrupted. When the resections are carried to the point *Y* on both sides, cardiac sensation appears to be entirely lost.

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15. Jonnesco, D., and Enarchesco, M.: Nerfs cardiaques naissant de la chaine thoracique du sympathique au dessous du ganglion stellaire, Compt. rend. Soc. de biol. **97**:977, 1927.

16. Braeucker, W.: Der Brustteil des vegetativen Nervensystems und seine klinische chirurgische Bedeutung, Beitr. z. Klin. d. Tuberk. **66**:1, 1927.

17. Kuntz, A., and Morehouse, A.: Thoracic Sympathetic Cardiac Nerves in Man, Arch. Surg. **20**:607 (April) 1930.

being no operation performed through the neck can safely reach below the lower part of the stellate ganglion; hence the presence of these lower structures may well account for the persistence of anginal attacks after cervical sympathectomy.

Figure 4 shows that after unilateral removal of the stellate ganglion, dogs tested by temporary occlusion of the descending branch of the left coronary artery gave distinct, painful responses. This, needless to say, shows that insufficient cardiac pain fibers had been interrupted.

3. *Unilateral Resection of Stellate and Upper Thoracic Ganglions.*—These dogs were subjected to the operation on the sympathetic ganglions from two to seven days previously. The operation was performed

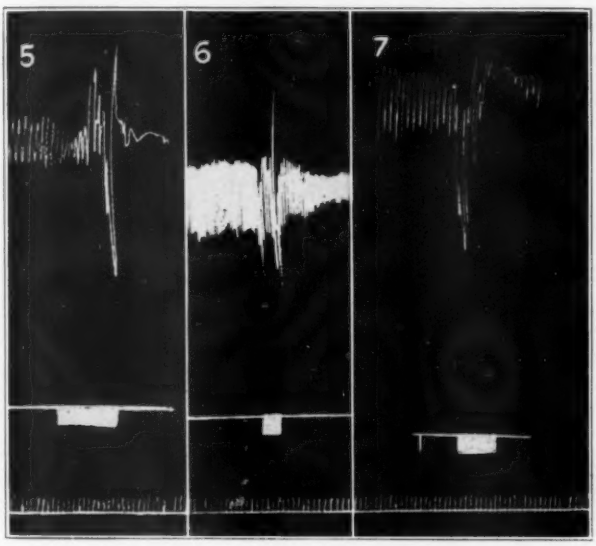

Fig. 4.—Cardiac pain transmission remained intact after resection of the left stellate ganglion in dog 5, the left stellate ganglion through the fourth thoracic ganglion in dog 6 and the left stellate ganglion through the fifth thoracic ganglion in dog 7.

under ether or pentobarbital sodium anesthesia. An incision was made high in the axilla. The pectoralis major and minor and the scaleni muscles were retracted forward. (The scaleni in the dog originate from the lateral surfaces of the upper four ribs as a broad ribbon of muscle.) This gave an excellent exposure of the upper ribs at their vertebral articulations. A 2 cm. section of the proximal portion of the second rib was then removed extrapleurally and the pleura pushed forward off the longus colli muscle. Through this approach the lower portion of the stellate ganglion can be picked up readily, and on cutting its rami the entire ganglion can be removed, along with the fibers of the annulus

of Vieussens up to the subclavian artery. By taking out a short section of the third or fourth ribs as well, the whole sympathetic trunk down to the fourth or fifth dorsal ganglions can be removed in one piece. This procedure can usually be carried out extrapleurally, but even if the pleura is opened, the dogs tolerate it well, provided the lungs are kept distended by blowing air down the trachea. When the scalenus muscle is sutured back in position, the leakage of air into the pleural cavity is stopped and the residual air can easily be removed by aspiration. This exposure gives an excellent view of the stellate ganglion and is particularly suited for careful dissection of the ganglions below.

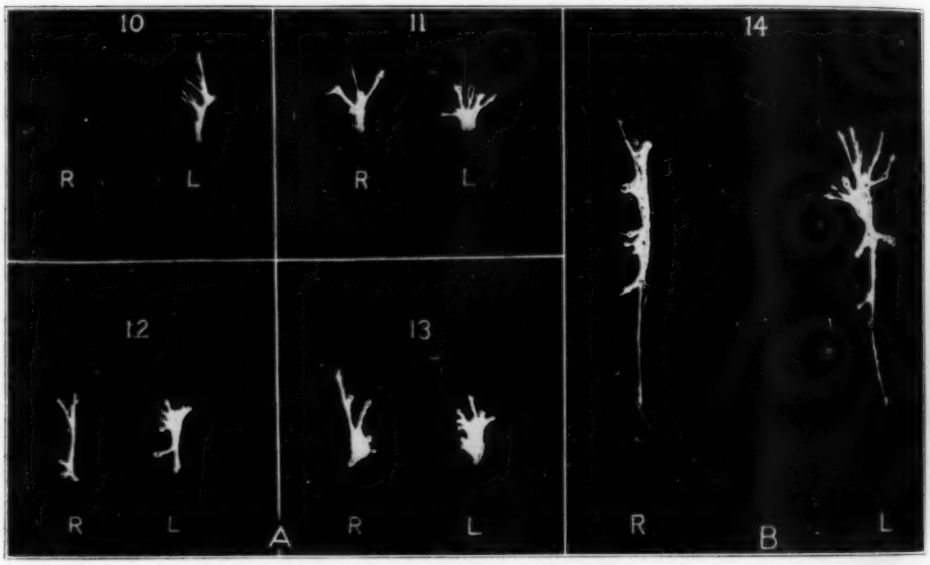

Fig. 5.—Ganglions resected in operations for angina pectoris: *A*, specimens from bilateral stellate ganglionectomy, the Jonnesco type of operation. Pain could still be elicited in five of six dogs. The specimen of the right stellate ganglion in dog 10 was lost. *B*, photograph of specimens after bilateral removal from the stellate ganglions down through the fourth thoracic ganglions. No pain could be elicited following this procedure.

After this procedure the operative incisions healed well, and the dogs were in perfect condition a few days later, when the pain responses were determined. Figure 4 (dogs 6 and 7) shows that even after such a radical procedure as unilateral removal of the stellate and upper four to five thoracic ganglions, cardiac sensation is still intact, although —as will be seen—it is probably limited to the side not operated on.

4. *Bilateral Stellate Ganglionectomy.*—This procedure amounts to the Jonnesco operation, as in carrying the dissection upward to the subclavian artery, all the sympathetic connections below the middle cervical

ganglion were removed. Figure 5 shows the extent of the resected nerves. Great care was taken not to injure the sympathetic trunk further down than its first dorsal ramus. By leaving the second dorsal ramus communicans intact, we were taking out as much as could be ordinarily reached through a cervical incision. In fact, it is a question whether more than the inferior cervical portion of the stellate ganglion is usually removed in this operation, as the operators frequently describe the excision of only a single ganglion, and the structure in man normally consists of two separate ganglions with an intervening isthmus. Figure 6 shows that five of six dogs gave distinct painful responses. Dog 11 showed no evidence of pain in his respiratory tracing, but to one observing his behavior it was obvious that he became somewhat restless at the time of stimulation. From these observations it is apparent that

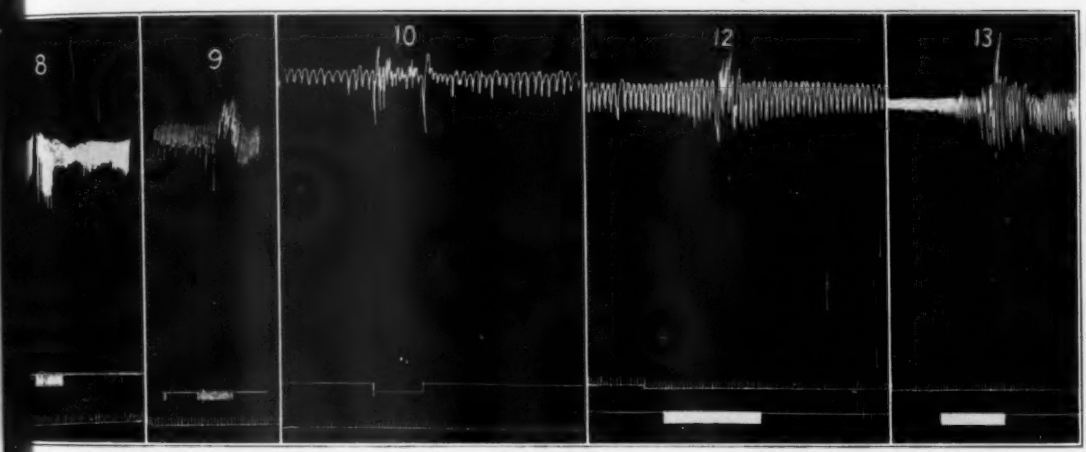

Fig. 6.—Respiratory tracings made following bilateral resection of stellate ganglions. They give clearcut evidence that cardiac sensation is still intact.

pain pathways exist after the complete removal of the lower cervical sympathetic and stellate ganglions on both sides. Do these pathways enter the lower thoracic ganglions through direct postganglionic connections with the heart, or do they reach the central nervous system through the vagus or by still other pathways? We hope to show by the following experiment that it is the recently discovered thoracic cardiac nerves which carry these residual painful stimuli.

5. *Bilateral Resection of Stellate and Upper Four Thoracic Ganglions.*—This operation was carried out in two stages (eight days apart) on an unusually irritable and sensitive young dog. Three days later the usual ligature was passed around the uppermost portion of the descending branch of the left coronary artery. Two hours after operation the dog was completely out of the ether anesthesia, walking

around the laboratory and interested in everything that was going on. On account of his playfulness, it was only with considerable difficulty that he could be induced to lie down and breathe regularly enough to produce an even kymographic tracing. Each time the coronary artery was occluded there was no sign of a response, either in the respiration or in the behavior of the dog (fig. 7). That he was extremely responsive to ordinary stimuli is shown at points in the tracing marked *B*, where the skin of the extremities was lightly pinched. This procedure bears out the results obtained by removal of these ganglions in the human being. One of us (Dr. White [18]) has reported the results of this operation on four human beings. In three of these there has been complete relief of pain on the side operated on, although anginal attacks remain unaltered on the other side. In the one case in which pain has persisted, it is present in a mild form and only over a small area in the arm. This is probably due to the fact that the stellate

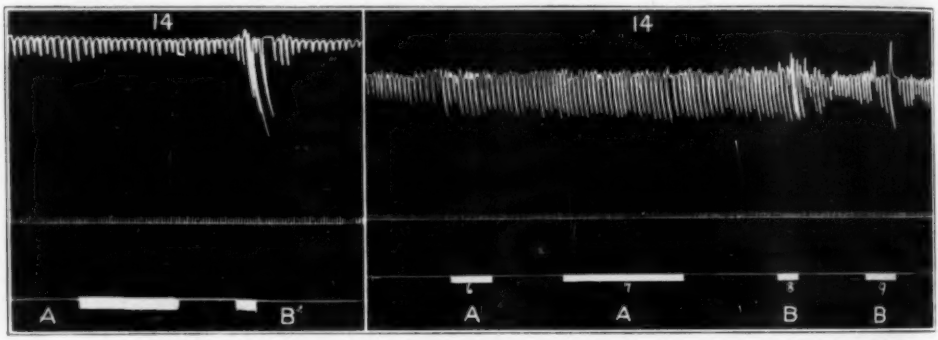

Fig. 7.—Respiratory tracings after removal of both stellate ganglions and the sympathetic trunks to the level of the fourth thoracic ganglions: *A*, coronary occlusion produced no evidence of any perception of the stimulus. *B* shows an immediate response to pinching of a toe pad.

ganglion was not wholly removed. In the cases of paravertebral injections of alcohol, in which these same fibers have been adequately blocked, there has also been complete relief of cardiac pain.

6. *Laminectomy and Section of Spinal Roots.*—In a series of five dogs the upper dorsal lamina were removed and a varying number of spinal roots were cut. Two or three days later the dogs, which appeared to have fully recovered from the effects of operation, were tested by temporary obstruction of the descending branch of the left coronary artery. Figure 8 shows that neither cutting the third to the seventh or

18. White, J. C.: Angina Pectoris: Treatment by Paravertebral Alcohol Injection or Operation Based on the Newer Concepts of Cardiac Innervation, Am. J. Surg. **9**:98, 1930.

the first to the fourth posterior roots on the left side nor cutting the upper four dorsal roots bilaterally prevented the sensation of pain. However, dog 18 (fig. 9) showed no signs of pain after the upper five anterior and posterior roots were cut bilaterally. In dog 19, in which the upper five posterior roots were cut bilaterally (with the exception of one small fiber of the third root on the right side), no symptoms of cardiac pain could be elicited.

These observations point out another possible method of relieving the pain of angina pectoris in man. There should be no need for cutting roots above the first thoracic, because, as pointed out, this is the highest segment that receives a white ramus communicans, and there are no higher connections between the cervical sympathetic trunk and the spinal cord. However, it is possible that in certain types of angina

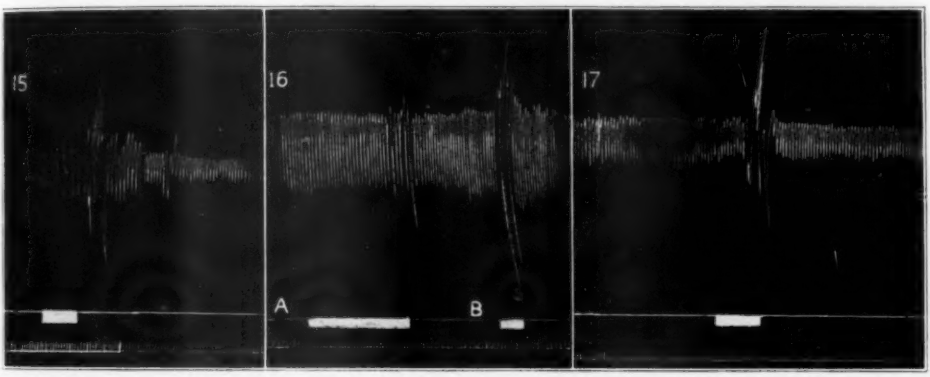

Fig. 8.—Results of cutting posterior spinal roots. Dog 15: Posterior roots, from third through seventh dorsal, cut on left. A marked response occurred to coronary occlusion. Dog 16: Posterior roots, from first through fourth dorsal, cut on left. A slight response occurred to coronary occlusion. (*A* indicates occlusion; *B*, pinching of a toe pad.) Dog 17: Posterior roots, from first through fourth dorsal, cut bilaterally. There was a definite response to coronary occlusion.

that are felt low down in the thorax or upper part of the abdomen, additional roots would have to be cut below the fifth thoracic segment.

7. Intercostal Neurectomy.—Weiss and Davis [19] have reported that in angina pectoris, as well as in other types of visceral pain, blocking of skin sensation entering the cord from any given area of referred pain may cause the pain to stop. One of the first methods of attacking angina pectoris surgically was by the section of intercostal nerves (Danielopolu [6]). This method was unsuccessful. In dog 20 (fig. 10) the upper five intercostal nerves on both sides were cut just distal to the point of origin of the sympathetic rami. This procedure was with-

19. Weiss, S., and Davis, D.: The Significance of the Afferent Impulses from the Skin in the Mechanism of Visceral Pain, Am. J. M. Sc. **176**:517, 1928.

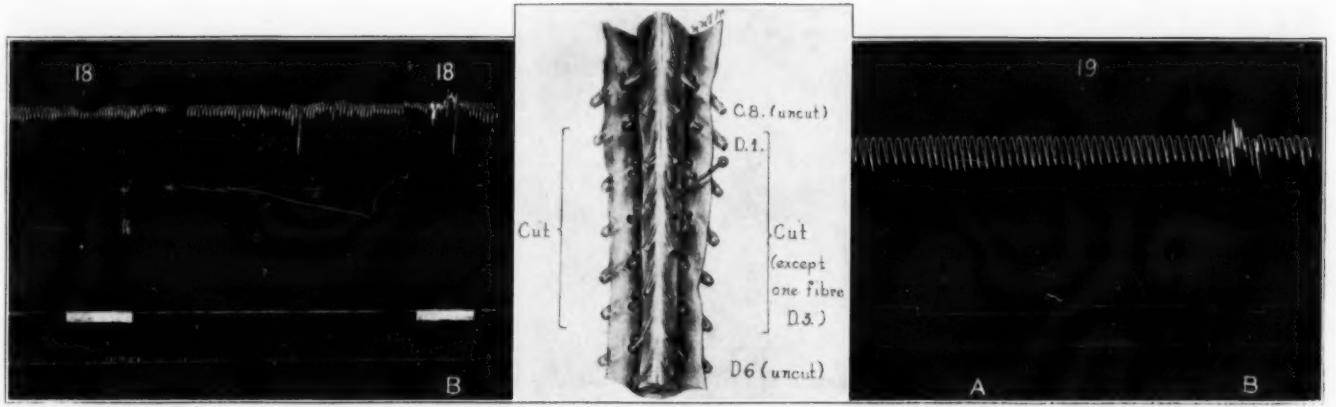

Fig. 9.—Respiratory tracings following operation. Dog 18: Anterior and posterior roots, from first through fifth dorsal, cut bilaterally. Dog. 19: Posterior roots, from first through fifth dorsal, cut bilaterally. The operation illustrated in sketch shows a single fiber from the third dorsal root, remaining uncut on right side. In none of these animals was there any pain sensation when the coronary artery was occluded (*A*). That normal skin sensation remained intact is shown by the response to light pinching of the hind toe pad (*B*).

out effect in preventing cardiac pain. Although this does not rule out the possibility that the dog might have felt visceral pain from afferent stimuli coming over the lower intercostal nerves, and that it might have been blocked if all these had been cut, this method could not be utilized for interrupting angina pectoris in man because it would be undesirable to cut such a large number of intercostal nerves.

8. *Bilateral Section of Vagus Nerves.*—It is a well known fact that the vagus nerve carries certain afferent impulses from the viscera to the central nervous system. In certain cases in which it has a well

TABLE 2.—*Efficiency of Various Neurosurgical Procedures in Interruption of Cardiac Pain Pathways in the Dog*

	Dog	Operation	Reaction to Occlusion of Coronary Artery
Controls	1		+++
	2		+++
	3		+++
	4		+++
Unilateral sympathectomy	5	Stellate (L)	+++
	6	Stellate through D4 (L)	+
	7	Stellate through D5 (L)	+++
Bilateral sympathectomy	8	Bilateral stellate	++
	9	Bilateral stellate	++
	10	Bilateral stellate	++
	11	Bilateral stellate	+
	12	Bilateral stellate	++
	13	Bilateral stellate	++
	14	Bilateral stellate, through D4	0
	15	Posterior root section, D3-D7 (L)	+++
	16	Posterior root section, D1-D4 (L)	+
	17	Posterior root section, D1-D4 (R and L)	+++
	18	Anterior and posterior root section, D1-D5 (R. and L.)	0
	19	Posterior root section, D1-D5	0
	20	Intercostal nerves, D1-D5 (R and L)	+++
	21	Division of vagi (R and L)	+++

defined depressor branch to the heart, Hofer [7] has reported good results from sectioning this depressor nerve. Other surgeons, however, have injected procaine hydrochloride directly into the vagi during attacks of angina pectoris, without relief. That bilateral section of the vagi has no effect on cardiac pain is clearly shown in figure 10 (dog 21).

In table 2 the effects on transmission of cardiac pain brought about by these various neurosurgical procedures are summarized. It is apparent that section of both vagi or of the upper intercostal nerves and resection of both stellate ganglions are inadequate procedures to control angina pectoris. Only removal of the stellates and upper four thoracic ganglions or section of the upper five spinal roots is capable of blocking cardiac pain completely.

EXPERIMENTAL METHODS FOR DETERMINING CARDIAC MOTOR PATHWAYS

Before the presence of direct connections between the upper thoracic ganglions below the stellate with the posterior cardiac plexus had been demonstrated anatomically by Jonnesco and Enarchesco,[15] Braeucker [16] and Kuntz and Morehouse,[17] Cannon, Lewis and Britton [20] had shown the presence of motor fibers running between these structures by physiologic methods. In their attempt to produce a completely denervated heart they continued to find marked degrees of cardiac acceleration after removal of both stellate ganglions, section of both vagi, denervation of the liver and removal of the adrenal medullas. It was only after the

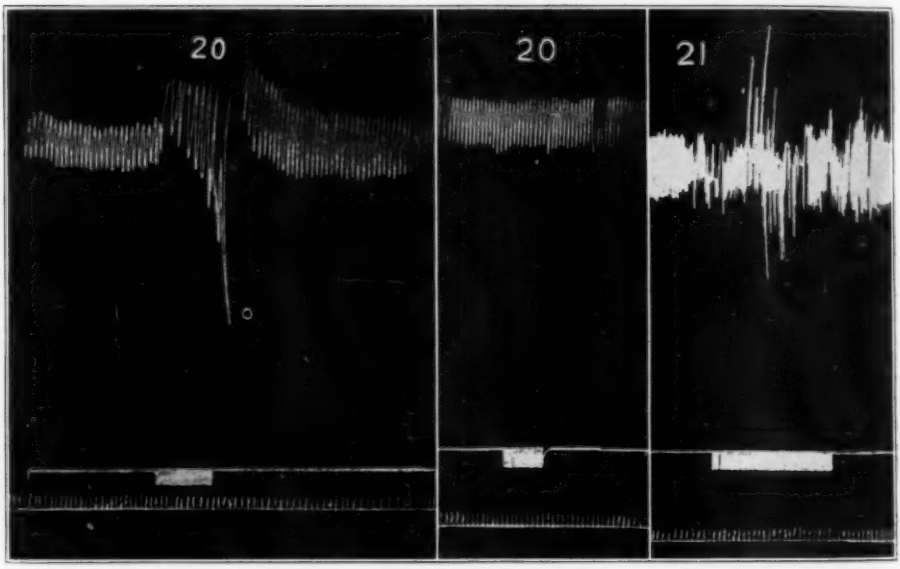

Fig. 10.—Respiratory tracings following operations. Dog 20: Bilateral section of upper five intercostal nerves just distal to the point of origin of the sympathetic rami. *A*, a marked response occurred to coronary occlusion. *B*, pinching of the skin over the upper thoracic wall proved anesthesia to have been complete. Dog 21: Bilateral section of vagi. Characteristic response on occlusion of coronary artery for twenty-five seconds.

upper thoracic ganglions had been removed on both sides that the heart failed to accelerate with emotional stimuli.

We have been able to show the presence of such connections by direct faradic stimulation of the ganglions. In a series of eight dogs

20. Cannon, W. B.; Lewis, J. T., and Britton, B. W.: A Lasting Preparation of the Denervated Heart for Detecting Internal Secretion with Evidence for Accessory Accelerator Fibres from the Thoracic Sympathetic Chain, Am. J. Physiol. **77**:326, 1927.

the upper sympathetic ganglions were exposed through the axillary incision already described. Pentobarbital sodium anesthesia was used in each case. Intratracheal insufflation of air prevented collapse of the lung in those cases in which the pleura was inadvertently opened. In the anesthetized animal the ganglions were stimulated intact and also after cutting the sympathetic trunk below the stellate ganglion. Stimulation was made both of the stellate ganglion above and the second and lower thoracic ganglions below. The stimulation was made with a tetanizing current produced by an induction coil, in which the secondary coil was set at distances varying between 7 and 10 cm. from the primary coil. With this arrangement there was no spread of current to the

TABLE 3.—*Results of Direct Faradic Stimulation of the Ganglions* *

Dog		Stellate				Second and Third Thoracic			
		Right		Left		Right		Left	
22	Heart rate.....	Not done		204-228	11%				
	Blood pressure	Not done		79-145	80%	Not done			
23	Heart rate.....	126-222	78%	162-228	40%				
	Blood pressure	83-111	33%	127-144	14%	Not done			
24	Heart rate.....	132-240	80%	138-216	58%				
	Blood pressure	98-144	47%	105-151	44%	Not done			
		(a) Cord Cut at C3		(b) Vagi Paralyzed		(c) Adrenals Cut Out			
25	Heart rate.....	147-258	75%	156-276	77%			156-300	92%
	Blood pressure	123-193	57%	114-131	15%			93-107	15%
26	Heart rate.....	105-198	88%	120-156	30%	111-114	3%	186-198	7%
	Blood pressure	161-187	16%	167-177	6%	160-150	—6%	176-164	—8%
27	Heart rate.....	144-168	17%	150-180	20%	156-180	16%	108-168	55%
	Blood pressure	154-206	32%	148-184	26%	165-205	24%	136-180	32%
28	Heart rate.....	87- 96	10%	126-132	5%	84-108	28%	99- 99	0%
	Blood pressure	126-135	7%	163-165	1%	141-128	—8%	158-160	1%
29	Heart rate.....	168-168	0%	174-180	4%	168-264	58%	168-234	39%
	Blood pressure	173-175	1%	166-164	—1%	163-175	7%	174-194	11%

* These figures represent the maximum responses obtained from faradic stimulation of the stellate ganglions and sympathetic trunk below. The trunk was cut between the first and second thoracic ganglions.

adjacent muscles. Stimulation was performed both with the vagi intact and also after both vagi had been sectioned in the neck or paralyzed with atropine. The blood pressure and heart rate curves were graphically recorded and the percentage increase in heart rate after stimulation computed as an index of cardiac acceleration. These findings are summarized in table 3.

Examination of these protocols shows that in animals stimulation of the stellate ganglion produced marked cardiac acceleration and often a considerable increase in blood pressure. It might be claimed that this pressor effect could have been brought about by afferent somatic stimuli ascending to the cerebral centers and causing a reflex vasoconstrictor response or by stimulation of the adrenals with an outpouring of epinephrine. To rule out these possible complicating factors, the

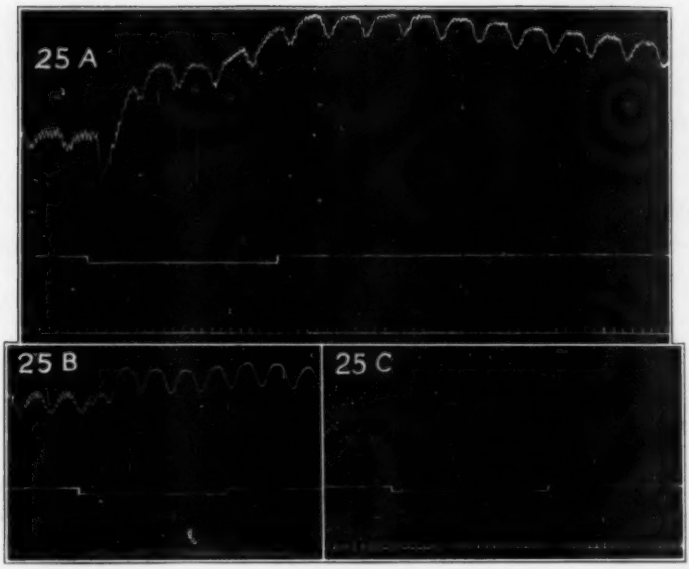

Fig. 11.—Cardiopressor response resulting from faradic stimulation of right stellate ganglion in dog 25. *A*, on stimulation after division of the spinal cord at third cervical segment, increase in heart rate, 75 per cent; in blood pressure, 57 per cent. *B*, on stimulation after paralysis of both vagi, increase in heart rate, 77 per cent; in blood pressure, 15 per cent. *C*, on stimulation after resection of adrenal glands, increase in heart rate, 92 per cent; in blood pressure, 15 per cent.

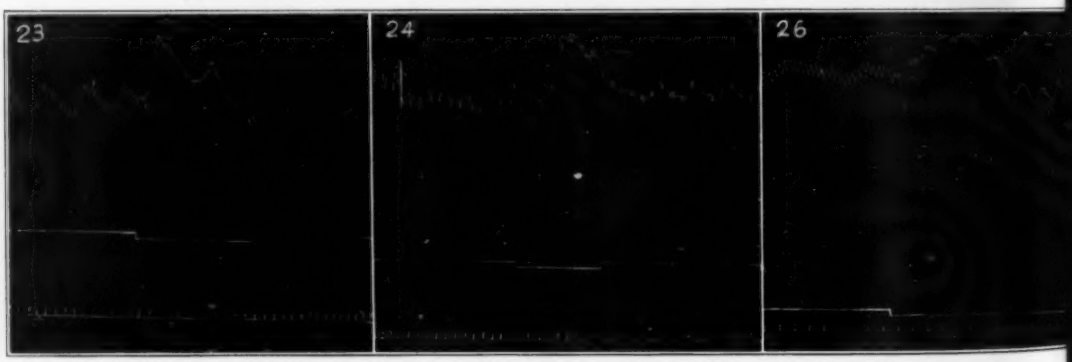

Fig. 12.—Cardiopressor response following faradic stimulation of the right stellate ganglion after division the sympathetic trunk at its lower pole and paralysis of the vagi with atropine (in this and the following figu the time signal at the bottom of the graph marks the base line for the blood pressure; the middle line marks duration of the stimulus: in dog *23*, increase in heart rate, 78 per cent; in blood pressure, 33 per cent. dog *24*, increase in heart rate, 80 per cent; in blood pressure, 47 per cent. In dog *26*, increase in heart r 88 per cent; in blood pressure, 16 per cent.

spinal cord was cut at the level of the third cervical segment in dog 25, and later both vagi were cut and both adrenal glands removed. It was possible to keep this dog in fairly good condition by maintaining pulmonary ventilation through an inspiratory and expiratory pump. With the dog's head lowered, the systolic blood pressure did not fall below 100 mm. of mercury. With all possibilities of sensory reflexes eliminated, the vagi paralyzed and the adrenals removed, this dog still showed a tremendous (92 per cent) acceleration of the heart when the sympathetic ganglions were stimulated (fig. 11). In most of these

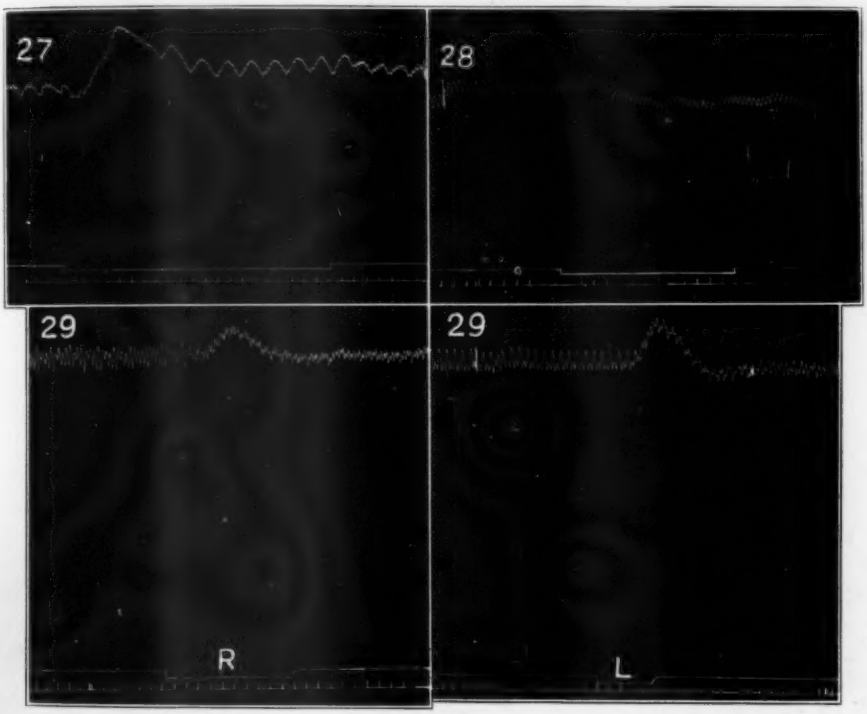

Fig. 13.—Cardiopressor response resulting from faradic stimulation of the second and third thoracic ganglions after removal of both stellate ganglions and paralysis of the vagus nerves with atropine. In dog 27, increase in heart rate, 55 per cent (left); in blood pressure, 32 per cent (left). In dog 28, increase in heart rate, 28 per cent (right); in blood pressure, —8 per cent (right). In dog 29, increase in heart rate, 58 per cent (right) and 39 per cent (left); in blood pressure, 7 per cent (right) and 11 per cent (left).

animals cardiac acceleration was greatest when the nerves on the right side were stimulated. No further increase resulted from bilateral excitation. The maximal acceleration of the heart rate on stellate stimulation was 92 per cent in dog 25 and from 88 to 78 per cent in dogs 23, 24 and 26 (fig. 12).

The maximal increase in cardiac rate when the lower thoracic ganglions were stimulated was 58 per cent. There was an acceleration of over 25 per cent on stimulating the lower ganglions in three of four dogs (fig. 13). It is furthermore interesting to note that in the cases of the greatest acceleration after stimulation of the lower ganglions there was a decided reduction of this response on stimulation of the stellate ganglions (dogs 27, 28 and 29). This phenomenon may well mean that while in a majority of cases the great preponderance of cardiac fibers run up through the stellate and the higher cervical sympathetic ganglions to reach the heart via the superior, middle and inferior cardiac nerves, in a smaller proportion of cases the lower transthoracic connections are of increased importance. In the first group cervical sympathectomy might well relieve the symptoms of angina pectoris, whereas in the second group relief would be slight or negligible. In summing up the results of these experiments on the cardiac accelerator pathways, it is again obvious that only an incomplete interruption of the pressor reflex can be achieved by limiting the operation to the removal of the cervical sympathetic down through the stellate ganglions. To interrupt effectively either the sensory or the motor pathways the operation must include the entire cervicodorsal ganglion and be continued down to the third or fourth thoracic segments.

COMMENT

While these experiments have definitely shown that in dogs there are important sensory and motor pathways connecting the heart with the spinal cord below the stellate ganglions, it is not necessarily safe to assume that these findings can be applied to man. In the clinical cases cited here, however, we have had a number of striking experiences which lead us to believe that the innervation of the heart in men and dogs is the same in all essential respects.

In approaching the problem of angina pectoris in man surgically, there are theoretically three possible methods of attack:

1. Vasomotor: Prevention of vasoconstrictor spasm of the coronary arteries.
2. Motor: Interruption of cardio-augmentor reflex.
3. Sensory: Interruption of pain pathways.

The physiologic studies of Anrep and Segall,[21] recently corroborated by Danielopolu,[22] rule out the first method. These writers have shown by a series of carefully worked out physiologic experiments that the vasoconstrictor fibers to the coronary arteries run in the vagus nerves,

21. Anrep, G. V., and Segall, H. N.: The Regulation of the Coronary Circulation, Heart **13**:239, 1926.

22. Danielopolu, D.; Marcou, I., and Proca, G. G.: Sur l'innervation des coronaires, Compt. rend. Soc. de biol. **107**:419, 1931.

Fig. 14.—Diagrammatic presentation of the peripheral innervation of the heart. The sympathetic fibers are drawn in red. It is important to note that the only connections with the spinal cord are over the white sympathetic rami from the upper five thoracic ganglions (illustration modified from diagram in White, Paul D.: Heart Disease, New York, The Macmillan Company, 1931).

whereas the sympathetic system carries vasodilator fibers. As it is impossible to cut both vagi, interruption of the vasoconstrictor fibers is out of the question. A common explanation of the benefits produced by Coffey and Brown's operation of superior cervical ganglionectomy has been based erroneously on the theory that it prevents vasoconstrictor spasm of the coronary arteries. Just what the mechanism of this operation is remains somewhat uncertain, as Holmes and Ranson [23] have produced histologic evidence that the superior cervical ganglions transmit no afferent fibers. On the other hand, Heinbecker [24] has shown characteristic afferent electrical discharges on testing this ganglion with a cathode ray oscillograph. In our clinic superior cervical ganglionectomy has given inferior results, as only three of eight cases have shown improvement and the mortality has amounted to 12.5 per cent. As few favorable reports have been published in the recent literature, it would appear that this operation is being less frequently used.

Concerning the interruption of motor impulses to the heart which drive it to exceed its limited capacity for work, our experiments show that to accomplish this completely it would be necessary to remove all the sympathetic ganglions on both sides from the inferior cervical down through the fourth or fifth thoracic. A bilateral excision would be necessary, because we have shown that stimulation of the ganglions on either side gives nearly equal cardiopressor response. If this were carried out, the heart would undoubtedly be greatly crippled. Danielopolu, in his writings, has even advised against removal of the stellate ganglions, recommending only the cutting of their postganglionic rami to the brachial plexus and vertebral artery. This point of view is probably over-conservative, as we have excised the cervicothoracic and second dorsal ganglions many times in Raynaud's disease with no evidence of impaired cardiac efficiency. This is probably due to the fact that sufficient cardiac accelerator fibers run directly from the third, fourth and fifth thoracic ganglions to the heart to enable it to respond to its physiologic demands. Our clinical observations have even shown that in the presence of advanced degenerative cardiac disease and angina pectoris all the cardiac nerve connections can be safely blocked on one side, allowing the nerves on the opposite side to regulate the activity of the heart.

We have always maintained that the logical point for surgical attack is the sensory pathway. If our arguments in favor of this method are substantiated, the next point to be considered is the most feasible method of interrupting the nerves which transmit cardiac pain. Figure 14

23. Holmes, W. H., and Ranson, S. W.: Surgical Sympathectomy in Angina Pectoris, J. Lab. & Clin. Med. **10**:183, 1924.

24. Heinbecker, P.: Recent Advances in Our Knowledge of the Sympathetic Nervous System, J. Thoracic Surg. **1**:233, 1932.

shows in diagrammatic form the anatomic arrangement of these fibers. In some cases the majority of painful stimuli probably traverse the middle and inferior cardiac nerves and can be reached through the old type of cervical incision. In other cases, however, severe pain can still enter the central nervous system by the lower pathways, which are out of reach of the operator who makes his incision in the neck. The surgeon who uses the cervical approach is under an additional handicap because of the complexity of the sympathetic nerve structures in this region and their frequent anatomic variations. Examination of the diagram shows that all of the cardiac fibers converge in the upper thoracic ganglions and then enter the spinal cord over the white communicant rami and the posterior roots. They can be completely interrupted by blocking either the ganglions, the rami or the spinal roots. All of these pathways are definite structures and show few variations in their arrangement.

In the Massachusetts General Hospital during the past five years twenty-seven patients with angina pectoris have been treated along the lines just described. The patients have been selected purely on the basis of the intensity of their pain, and only those have been accepted who have not responded to medical treatment and who have continued to suffer so severely that they felt that the pain was unendurable. Neither the history of recent coronary occlusion nor active decompensation has been considered as a contraindication to the injection of alcohol. While surgical excision of the upper thoracic ganglions has given nearly perfect relief of pain on the side of operation,[25] this is probably too dangerous an operation to be used in patients with advanced coronary disease. Although there have been no early postoperative fatalities, two out of four patients have died within a month of operation, one of empyema following pneumonia and the other of coronary occlusion. The paravertebral injection of alcohol, on the other hand, is a reasonably safe surgical procedure. The results in these cases are summarized in table 4. Examination of this table shows that the method is capable of giving nearly complete relief in half the cases and of converting the severe forms of angina pectoris into milder types which can easily be controlled by medical measures in another 30 per cent. In the remaining 20 per cent of cases pain has not been satisfactorily relieved. In each of the latter complete anesthesia of the intercostal nerves has not been produced and it has been evident that failure has been due to the technical difficulty of performing a perfect injection. Our statistics here are in accord with those of other clinics and show that injection of alcohol

25. Our clinical experience has shown without exception that alcohol block or resection of the ganglions on a given side is capable of relieving cardiac pain on that side only. There is no justification for the belief that sympathectomy should be performed on the right side when it has failed to relieve the attacks on the left.

is undoubtedly the safest surgical method of treating angina pectoris and one which rests on a sound physiologic basis. Owing to the inherent difficulties in the technic, about one case in five is doomed to failure. It is also only fair to point out that following injection there is usually a transitory period of alcoholic neuritis of the infiltrated intercostal nerves. This may last from a few weeks to several months, and is particularly annoying in the cases in which a satisfactory result is not obtained.

In those cases of paravertebral injection of alcohol which fail, it would be difficult to carry out a dorsal ganglionectomy because the fibrosis produced by alcohol makes freeing of the pleura and exposure of the ganglions extremely difficult. Our experiments on animals show, however, that these cases can still be relieved by cutting the posterior spinal roots. This operation was recently performed by Loyal Davis [26] and was a complete success.

TABLE 4.—*Results of Twenty-Three Paravertebral Injections of Alcohol Performed in Massachusetts General Hospital* *

	Per Cent
Good (100 to 90% relieved)	47.8
Fair (90 to 50% relieved)	30.4
Improved (50 to 25% relieved)	8.7
Failures	13.1
Deaths	0
Complications: troublesome intercostal neuritis	13.0

* These cases have been followed from five years to six months.

We hope that this study of the sensory and motor pathways of the heart will be taken as a mere beginning toward a physiologic understanding of the surgical problem of angina pectoris. With the recent advances in the anatomy of the cardiac nerves and the development of a method of producing the condition experimentally in animals, a more rational surgical therapy should soon evolve. A start has now been made along these lines, but much further clinical experience will be required to substantiate these theories completely.

SUMMARY AND CONCLUSIONS

1. Through the use of Sutton and Lueth's method of temporarily occluding a branch of the left coronary artery in dogs, we have found that the resulting ischemia of the heart muscle can be counted on to produce characteristic changes in the behavior of the animal which closely resemble the manifestations of angina pectoris in man. We have employed this procedure in a series of twenty-one dogs to test the effectiveness of various neurosurgical operations for interrupting the pathways of cardiac pain.

26. Davis, L.: Personal communication to the authors.

2. As a result of these experiments, it has been shown that cardiac pain is not transmitted by the vagus nerves. It is not prevented when afferent impulses from the areas to which cardiac pain is usually referred are blocked by sectioning the upper intercostal nerves on both sides. Bilateral resection of both stellate ganglions may diminish, but does not block, all sensory stimuli from the heart. A distinct sensory response has been obtained in five of six animals in which this operation has been tested.

3. Bilateral removal of the sympathetic ganglions from the stellate down through the fourth thoracic ganglion or section of the upper five posterior dorsal nerve roots appears to interrupt all sensation from the heart.

4. We have also shown that the motor pathways to the heart cannot be completely destroyed by bilateral excision of the stellate ganglions. The upper thoracic ganglions below the stellate ganglion send important motor, as well as sensory, fibers directly across the posterior mediastinum to the posterior cardiac plexus. When these are stimulated electrically the heart rate may be augmented as much as 58 per cent.

5. We believe that these experiments explain the frequent failures and poor results of the many different modifications of cervical sympathectomy which have been recommended for the relief of angina pectoris. No cervical sympathectomy can produce either a complete sensory or motor denervation of the heart. No operation performed through a cervical incision can give a satisfactory exposure for the excision of these important lower ganglions or the section of their communicant rami.

6. In four patients in whom the upper dorsal ganglions were resected through a posterior thoracic approach, the relief of angina pectoris has been satisfactory. The operative risk involved, however, is too great for the routine use of this procedure.

7. For the routine treatment of angina pectoris we recommend paravertebral injections of alcohol into the upper four to five thoracic ganglions and their rami. In a series of twenty-three patients treated in this clinic injection has given excellent results in 50 per cent. Intractable angina pectoris has been reduced to a much milder form, which can be easily handled by routine medical measures, in another 30 per cent. In the remaining 20 per cent of failures, the poor result has been obviously due to incomplete blocking by the alcohol.

8. Our experiments on animals indicate that the patients who fail to gain relief by this relatively safe procedure can still be relieved by section of the upper thoracic spinal nerve roots.

BONE GROWTH AND PATHOLOGY AS SEEN IN THE FEMUR (AND TIBIA)

VII. STUDIES ON THE FEMUR

N. WILLIAM INGALLS, M.D.
CLEVELAND

A little more than twenty years ago, Dr. Hamann [1] described and illustrated a most remarkable condition in the skeleton of the lower limbs, involving most conspicuously the femora. The specimen in question, now E 386 of the Hamann Museum, is still in many ways an enigma, and apparently is quite as unique as when described for the first time by Dr. Hamann.

My reasons for reviving this subject are briefly as follows: The original account of these femora was characteristically brief and concise, and it concerned itself only with the more essential and significant features; however, the rarity of the condition and its apparent significance seem to call for a more extended consideration. In addition to this, I believe that it is possible to offer something in the way of explanation. Before detailing my own observations on these bones, I shall quote most of the original article verbatim; except for what is noted here, there is no history (fig. 1).

> Two femora in my possession present a variation in the configuration of the lower half of each bone that is certainly unusual and to my knowledge has not been described. The bones were taken from a tall, thin, male adult who had apparently died of tuberculosis. There are no abnormalities in the other bones, with the exception that the upper thirds of both tibiae are rather thicker in the transverse diameter and the curves in the bone are somewhat greater than is normal.
>
> The femora are perfectly symmetrical: the surface of the bones is smooth and there is no evidence of periosteal or osteal inflammation; the articular extremities show no evidence of disease. At about the middle of the shaft, each femur begins gradually to flatten anteroposteriorly and the transverse diameter increases till the condyles are reached, thus differing markedly from the more rounded form of the normal femur. A transverse section of the bone would therefore present a transversely oval form.
>
> These bones do not correspond in shape or appearance to any of the pathologic modifications of the femur that have been described, indeed as stated above there is no evidence of any inflammatory or hyperplastic process. The density of the bone seems normal; no section has been made to show the interior, however.

From the Anatomical Laboratory, Western Reserve University.

1. Hamann, C. A.: An Abnormality in the Form of the Femur, Cleveland M. J. **9**:710, 1910.

The specimens, I believe, are to be regarded as a variation in the normal form of the femur; in other words, as anomalies; whether or not any morphologic significance is to be attributed to them, I do not know. The marked symmetry is an interesting feature.

In comparing the condition of the femora of E 386 with normal or average conditions, I shall refer to my previous observations on the

Fig. 1.—Bones of the right lower extremity of E 386.

femur which were based on 100 pairs of bones, from white men, dissecting room material, and shall use the mean values of the combined right and left sides, 200 bones in all (Ingalls,[2] 1924).

2. Ingalls, N. W.: Studies on the Femur: I. General Characters of the Femur in the Male White, Am. J. Phys. Anthrop. **7**:207, 1924.

EXTERNAL FEATURES

Except for their outward form and proportions, the bones of E 386 show nothing out of the ordinary on external examination. They are clean, hard, normally smooth and much whiter than most of our specimens, but with no evidences of inflammatory processes or other pathologic changes in the tissue; only in the upper part of the tibiae is there a slight roughening on the lateral surface. Indeed, one of the most striking features in regard to these bones is that the conventional anthropologic measurements, if unaccompanied by illustrations, would

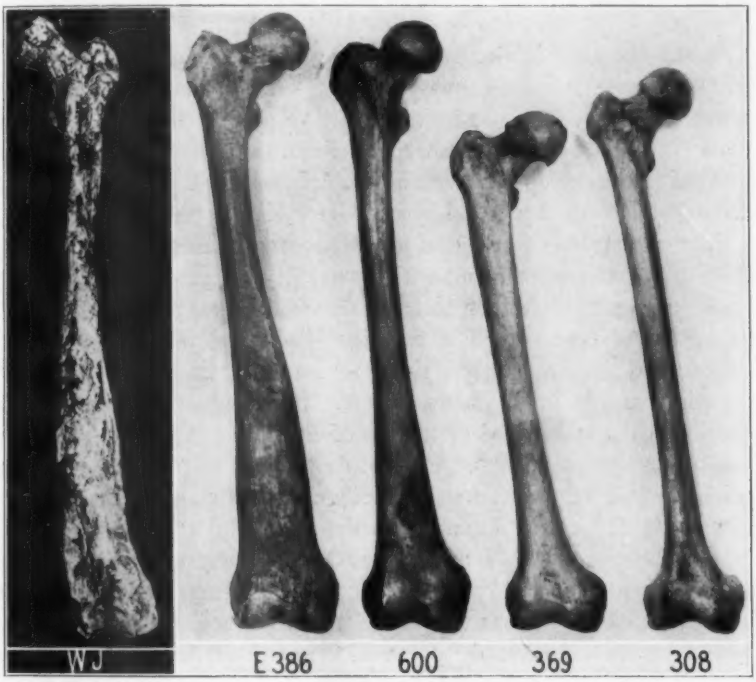

Fig. 2.—Series of femora to illustrate the varying configuration of the lower part of the shaft. *369* represents average conditions as far as the distal diaphysis is concerned. *308* shows a narrow lower end, which part, in *600*, is very broad. On the left (*W J*) is a reproduction of the Nubian femur, reported by Wood Jones, mentioned in the text; its length here is the same as that of *E 386*.

have given no indication whatever of the remarkable conditions obtaining in them. Except for the conspicuous enlargement in the lower part of the femur and the upper part of the tibia, there is nothing in these bones to attract attention.

The femora are quite long; the oblique length, measured in the natural position of the bone, is 514.5 mm. on the right and 516 mm. on the left, about 50 mm., or 2 inches (5 cm.) above the average, but definitely

below the maximum of our series of 100. The right tibia has a maximum length of 448 mm.; the left is a trifle shorter, 447 mm.; not only are the tibiae very long, but they are probably disproportionately long for the femur. Both the femur and the tibia, we believe, are definitely longer than they would have been if their normal growth had not been disturbed, but the overgrowth seems to have affected the tibia rather more than the femur. In both cases, moreover, the extra length seems to have been added in that part of the bones adjacent to the knee joint, rather than being more evenly distributed throughout. Since the bones of both the right and the left side present practically identical features I shall not make any special reference to either side.

As may be seen in the accompanying figures (figs. 1, 2 and 3), the lower femoral shaft, in somewhat more than half its extent, shows a marked increase in width; its internal border, just below the center of the bone, is also much more sharply convex than usual, and at the same time the anteroposterior dimensions are definitely increased. The unusual, and really abnormal, proportions of this part of the diaphysis are most clearly brought out if the transverse diameters are compared with certain other dimensions which are still perfectly normal. For this purpose the epicondylar, or bicondylar, width is especially useful, since it is measured transversely across the bone, just below the region in question, and also because it is the most constant, least variable measurement which can be taken on the femur. Omitting actual figures, it may be said that the transverse diameters of the lower diaphysis in this case are approximately 50 per cent above those seen in the average, normal specimen. For example, in the average bone the transverse diameter of the shaft, from 4 to 5 cm. above the margin of the articular surface in the midline, is about 41 mm.; in E 386, this measurement is 62 mm. The anteroposterior thickening is much less pronounced. If the posterior aspect of the bone is examined, it will be seen that the apex of the popliteal surface, indicated by the divergence of the lips of the linea aspera, is much higher in this bone than is usually the case. In the average femur the popliteal apex is a little over 120 mm. above the posterior border of the intercondylar notch. In our specimens it is in the neighborhood of 200 mm., for this is at best a rather uncertain measurement. It is this enormous increase in the popliteal length which, in conjunction with other characters, led us to suspect that the lower end of this bone is not only too wide but also much too long, as if the distal third had been stretched out to make the distal half. The abnormalities displayed by E 386 are sharply restricted to the lower diaphysis; the remainder of the bone, including the immediately adjacent knee joint, shows nothing which can be interpreted as abnormal or aberrant.

Much less will be said in regard to the tibia, since our acquaintance with this bone is rather less intimate and extensive than in the case of

the femur. Its proximal portion, almost if not quite half, is evenly and uniformly expanded, the increase in dimensions being rather more conspicuous in the transverse than in the sagittal diameter. In addition to this enlargement there is also a marked bowing of the bones, the most prominent part of the convexity being on the inner side just above the center. Except for being somewhat massive, in this respect matching the tibiae very well, the fibulae show no unusual characteristics.

In our series of 100 pairs of femora referred to, a few cases were encountered which showed a conspicuous widening of the lower shaft, e.g., specimen 600 (fig. 2), but nothing approaching either the absolute

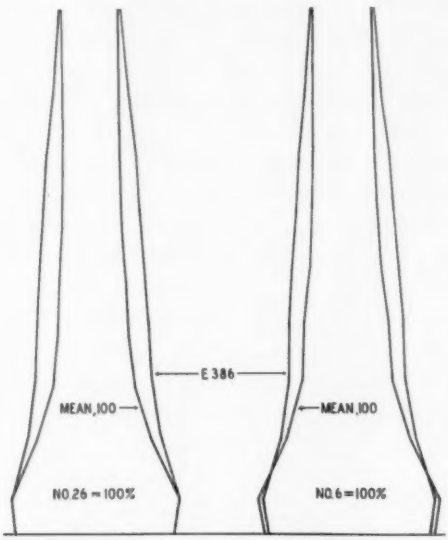

Fig. 3.—Schematic outlines of the lower half of the femur for *E 386* and for the mean values of our series of 100. On the left the dimensions are in terms of the same epicondylar breadth, *N. 26;* on the right, in terms of the same diaphyseal length, *No. 6.* It will be seen that the deviation in *E 386* are confined to the lower part of the shaft.

or the relative proportions exhibited by E 386. We do not believe that specimen 600 is quite normal and would place it with E 386, not necessarily because of any common pathologic condition, but because the disturbance, whatever it may be, has picked out the same part of the bone. The only case in the literature, so far as we know, which might be compared with ours was found by Wood Jones in ancient Nubian material (fig. 2). "In body 45 : 240, an adult man of the archaic period from the large cemetery at Dehmit, the left femur and tibia had undergone a very remarkable change. The lower half of the femur and the

upper half of the tibia have become greatly enlarged and thickened."[3] In this case the surface of the bones was roughened and irregular, but the knee joint was not involved. Apparently the condition was unilateral in this case, something one would hardly expect, but of this we cannot be certain. The rarity of this condition is indicated by the fact

Fig. 4.—Frontal section of the left femur of *E 386* and a control section of the femur of approximately the same length, to show the excessive amount of cancellous bone and the short medullary cavity.

that it was unique among 6,000 bodies; for this reason also the suggested diagnosis of syphilis was considered to be rather hazardous.

3. Smith, G. E., and Jones, F. W.: The Archaeological Survey of Nubia: Report for 1907-1908; Report on the Human Remains, Cairo, 1910, vol. 2, p. 289, plate XLVIII, fig. 4.

INTERNAL ARCHITECTURE

Longitudinal sections through the left bones of E 386 show that the disturbance in this case has affected the entire thickness of the shaft, from the center to the periphery (fig. 4). The conditions found were quite unsuspected and were not known at the time of Dr. Hamann's original description. The most striking feature presented by these sections is the enormous amount of cancellous bone and the extremely small, short, medullary cavity. Ordinarily, the medullary cavity of the femur extends throughout most of the shaft, although its extent seems to be subject to considerable variation. Variable also are the amount, character and arrangement of the spongy bone which bounds the cavity and which may encroach on it to a considerable extent. From the specimens we have examined, it would appear that the upper limits of the marrow cavity are rather more definite and constant near or just below the lesser trochanter than they are at the lower end. In some cases the cavity extends below, almost to the old epiphyseal line, while in others it terminates at a much higher level. In E 386 the medullary cavity is only about 8 cm. long, not over a third of what might be found in much shorter bones; it is also situated high up, above the center of the shaft, and its limiting walls show unusual amounts of spongy bone. The dense bone of the shaft, at the level of the marrow cavity, is thicker than in most bones, while the cortical layer in the distal portion is thinner. This thinning of the cortex below is doubtless due to the great mass of internal cancellous tissue which makes a normally thick, supporting cortex unnecessary. Extending axially through the cancellous tissue which fills the lower half of the bone there is a broad zone, obviously a continuation of the marrow cavity, in which the spongy bone is somewhat less dense than elsewhere and is distinctly more irregular in structure.

Similar conditions obtain in the tibiae. The marrow cavity is little, if any, longer than in the femur; here, as contrasted with the femur, the cavity is below the middle of the bone, the proximal half being filled with cancellous tissue a little less dense than that in the bone above.

The only significant features in regard to this cancellous tissue are the increase in amount and density and the restriction of these changes to the portions of the bone immediately adjacent to the knee joint. While it can hardly be said that the osseous tissue involved is pathologic or abnormal in any way, there are certain secondary changes in the spongy bone which seem to be the direct result of the greater amount of bone present. These changes manifest themselves as a greater irregularity in the cancellous architecture, and one misses, to some extent, the characteristic disposition and arrangement of the finer osseous lamellae, particularly in the upper end of the tibia. The reasons for this

would seem to be quite simple, for in this case, with a marked excess of supporting osseous tissue, there is not the call for its economical distribution in relation to the predominating physical strains and stresses.

ETIOLOGIC FACTORS

While it is possible that the bones that have been considered may depart in some way from the normal in their finer histologic structure or chemical composition, the most obvious disturbance is in the amount and disposition of bony tissue. In both femora and tibiae there has been an alteration in form and length, there has been an excess production of building material, and all of these changes have come about at one end, instead of being more evenly distributed. The fact that the conditions are bilateral and perfectly symmetrical is of particular significance. What the etiologic influences may have been, we cannot say; most likely we are dealing with a deep-seated, chronic derangement, possibly metabolic or in part endocrine, which has disrupted entirely the normal growth and differentiation in the distal femur and proximal tibia.

Although we have no suggestions to offer as to the etiology of the conditions described, we believe that it is possible to present evidence as to why these particular parts of the bones have been picked out. What the remainder of this skeleton might have been like, we do not know.

In one of our recent articles on the femur,[4] we called attention to the fact that the lower portion of the femoral shaft, particularly in its transverse diameter, is the most variable part of the bone. The variability here is about twice as great as it is a few centimeters below, across the condylar region, and is distinctly higher than it is in the middle of the shaft. This unusual variability may be explained as one of the results of the comparatively recent remodeling and readjusting that have taken place in the neighborhood of the knee joint in association with the assumption of the erect posture. The extensive and characteristic alterations that have been instituted in the phylogenetic development of the human knee, changes which have involved the soft parts, muscles, ligaments, etc., no less than the skeletal elements, have left this whole region, both structurally and functionally, in a distinctly unstable and vulnerable condition, and this susceptibility and vulnerability are especially in evidence in the lower femoral shaft. There is also evidence that the proximal portion of the tibia shares somewhat in the same general condition and for the same reasons.

An important aspect of this relative vulnerability, which in turn is an expression of the newness and as yet unstabilized conditions around

4. Ingalls, N. W., and Grossberg, M. H.: Studies on the Femur: VI. The Distal Part of the Diaphysis, Am. J. Phys. Anthrop. **16**:475, 1932.

the knee, is the comparative frequency with which this part of the femur deviates more or less from normal and average conditions. Often enough these deviations take on a frankly pathologic character, and pathologic changes in the femur are usually found in the lower part of the shaft, in the tibia near its upper end. Specimen E 386, we believe, represents one of those cases, and they are by no means rare, in which definitely pathologic processes manifest themselves, frequently or by preference, in those organs or structures the phylogenetic past of which has left them relatively variable, unstable and vulnerable. A comparable state of affairs exists in the lumbar spine, also a region recently modified to suit the upright position, and here, again, defects and divers infirmities are especially frequent (Willis,[5]).

Additional data on E 386, more from the anthropologic point of view, and further comments on the general subject of femoral variability will be found in the article previously mentioned.[4]

5. Willis, T. A.: Backache from Vertebral Anomaly, Surg., Gynec. & Obst. **43**:658 (May) 1924.

USE OF RIB GRAFTS FOR FUSION OF THE SPINAL COLUMN

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CHICAGO

From the beginning of reconstructive and plastic bone surgery ribs have been transplanted not infrequently to promote union between bone fragments, to bring about fusion of adjacent bones and to bridge defects resulting from the loss of substance. Of their use in this latter rôle, Eloesser,[1] in 1920, contributed his experience with twenty-two cases involving bones of the extremities. He concluded that rib grafting was a feasible procedure, that ribs are more likely to survive in the presence of infection than the more dense massive grafts, that they are rapidly absorbed, and that they are particularly useful when no great demands are made on the strength of the graft (until replaced by new bone). He also observed that when used to repair large defects or when put under strain they were more prone to refracture than (full thickness) tibial grafts.

The first reference to the use of rib grafts for fusion of the spine was reported by Gutierrez[2] in 1924. In his six cases of vertebral tuberculosis, solid bony fusion was obtained, with subsequent arrest of the disease. Similar experiences were reported by Grantham[3] in 1927 and by Casacescu[4] in 1929. In the same year Whitman[5] and Kleinberg[6] reported the transplantation of ribs for osteosynthesis of the spine in cases of scoliosis. The ribs were removed primarily to reduce the posterior bulge of the thoracic cage resulting from the rotation of the spine. In most instances, as in the references noted, the grafts were preserved and transplanted at a second operation. From an experience with fifteen cases, A. Whitman[5] reported that the rib grafts were "rapidly replaced by an unusually heavy deposit of bone."

From the Department of Surgery, the University of Chicago.

1. Eloesser, Leo: Rib Grafting Operations for the Repair of Bone Defects and Their End-Results, Arch. Surg. **1**:428 (Nov.) 1920.

2. Gutierrez, A.: Rib Implant in Tuberculous Spondylitis, Arch. franco-belges de chir. **27**:768, 1924.

3. Grantham, S. A.: Method of Spinal Fixation in Tubercular Spondylitis in Children, J. Bone & Joint Surg. **9**:748, 1927.

4. Casacescu, H.: Spinal Bone Grafts with Multiple Fragments of Ribs in Pott's Disease, Rev. de chir., Bucuresti **21**:143, 1929.

5. Whitman, A.: Rib Grafting for Scoliosis, Am. J. Surg. **6**:801, 1929.

6. Kleinberg, S.: Spinal Fusion in Scoliosis, J. Bone & Joint Surg. **11**:66, 1929.

The most important considerations in the selection of bone for transplantation are the relative inherent osteogenic properties and tensile strength. The latter factor is of no great consequence in the type of operation to be described subsequently.

COMPARATIVE OSTEOGENESIS

In comparing the respective osteogenic potentialities of ribs (cancellous bone) with the dense cortical bone of tibial grafts reference will be made to experimental observations reported in the literature and to some which were personally conducted. All observers are agreed that spongy bone undergoes absorption and is replaced by new bone sooner after transplantation and more rapidly than dense cortical bone. Their opinions diverge only in respect to the explanation of the phenomena as based on the two principal theories of osteogenesis.

In regard to the transplanted bone in animals, Gallie and Robertson,[7] advocates of the cellular theory, made the following observations:

> The changes observed (in cancellous grafts) resemble those already described (compact bone) except that they have occurred much earlier and much more extensively. The bone cells in the lacunae all die and disappear, as described before, but the circulation is fairly well reestablished in one week. Not only do the surface osteoblasts survive, but the osteoblasts in the open Haversian canals for a considerable distance inward from the surface continue to live and functionate so that at the end of three weeks absorption is taking place in all directions through the graft and new bone not only surrounds the graft on its external surfaces but extends throughout its whole length and thickness. The picture is in marked contrast to that of the compact graft of similar age. Not only is this increased rapidity of absorption and replacement due to the increased number of active cells present, but it is also due to the greater ease with which the new blood vessels and osteoblasts can advance from the periphery to the center.

They believe that a greater number of cells survive because spongy bone is more cellular and more permeable to the nutrient lymph in which it is bathed. For this reason they stated that:

> Theoretically the best bone to use would be cancellous bone such as a rib. But unfortunately this activity is directed primarily in the direction of absorption so that rib must not be used if any great strain is to be placed on it (where the gap to be filled is large).

Leriche and Policard,[8] exponents of the noncellular theory, stated that "transplants of spongy bone take better than do those of compact bone. The passage ways for the rehabilitation are larger and more per-

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7. Gallie, W. E., and Robertson, D. E.: The Repair of Bone, Brit. J. Surg. **7**:211 (Oct.) 1919.

8. Leriche, R., and Policard, A.: The Normal and Pathological Physiology of Bone: Its Problems, translated by Sherwood Moore and J. Albert Key, St. Louis, C. V. Mosby Company, 1928, pp. 124 and 166.

meable. . . . " They also stated that "all transplanted bone fragments die, resorb, and it is uniquely in dying that bone gives rise to new bone." Although less calcium is transplanted with cancellous bone, it is more accessible for liberation by the osteoblasts, and in consequence a "calcific surcharge" to the "ossifiable medium" is rendered earlier and more rapidly. To these views, in general, Bancroft,[9] Greig,[10] Murray[11] and others subscribe.

In an endeavor to compare the relative osteogenic properties of rib with tibial transplants with specific reference to their use in spinal fusion operations, two types of investigation were carried out, clinical and experimental.

CLINICAL HISTOLOGIC STUDIES

Since adequate fixation of a scoliotic spine frequently requires fusion of twelve or more vertebrae, the operation at the University of Chicago Clinics has usually been performed in two stages with an interim of approximately two weeks. From six of such cases sections of grafts placed at the first operation from ten to fourteen days previously were removed in the course of the second stage for histologic study. In each instance the graft had the appearance of dead bone, but was firmly fixed in edematous fibrous tissue to the bed of bone chips in which it had been placed.

These specimens, two of costal and four of tibial transplants, were decalcified and sectioned. In all instances the surfaces of the grafts were partially or entirely covered by loose cellular tissue with numerous round, fusiform and polygonal cells with long protoplasmic processes and an occasional multinucleated cell occupying a small cavity on the surface of the bone. In the open haversian canals on the free end of all grafts and about cancellous spaces of the ribs there was evidence of osteoblastic proliferation and an ingrowth of newly formed connective tissue with a network of capillaries. With the exception of one tibial graft there were small areas of fine trabeculae of new bone on both surfaces and in one rib graft, in several cancellous spaces. Definitely more new bone was present in the rib specimens.

The bone itself had essentially the appearance of necrosis. The lacunae were either empty or contained cells that were markedly shrunken and stained poorly. Except for a narrow peripheral border of living and proliferating cells, the blood vessels and cellular tissue were coagulated and undergoing autolysis. There was very little, but definite, evidence of beginning bone absorption.

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9. Bancroft, F. W.: Bone Repair Following Injury and Infection, Arch. Surg. **5**:646 (Nov.) 1922.

10. Greig, D. M.: Clinical Observations on the Surgical Pathology of Bone, Edinburgh, Oliver & Boyd, 1931.

11. Murray, C. R.: The Repair of Fractures, Minnesota Med. **13**:137, 1930.

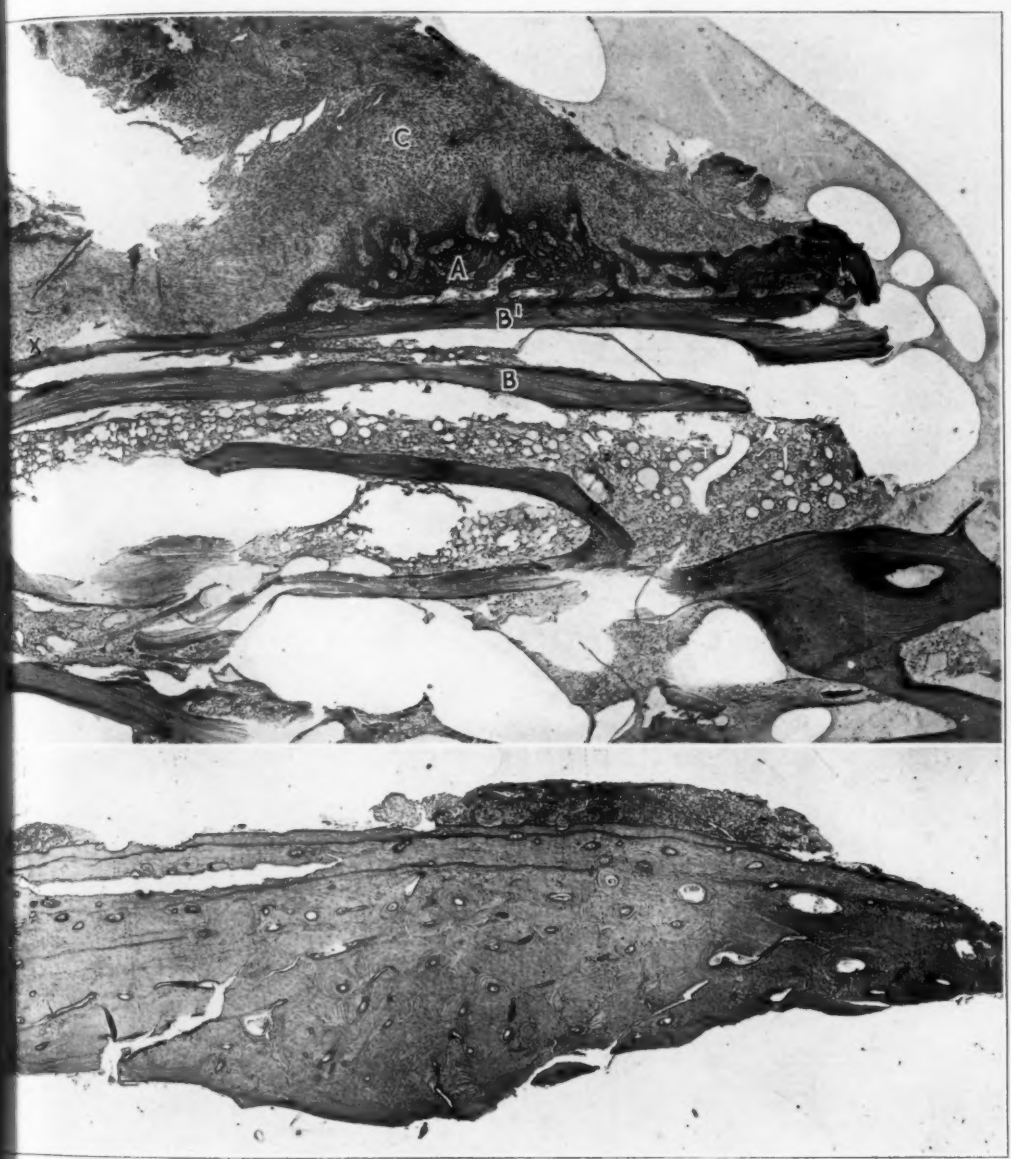

Fig. 1.—The upper photomicrograph shows a specimen from a thirteen day human rib graft in which superficial bone cells survived transplantation. *B'* represents the area in which these cells were found (see fig. 2). *A* shows the new bone overlying it; *C*, osteoid tissue; *B*, necrotic bone, and *X*, the area in which there were no living bone cells and no overlying new bone. Reduced from a magnification of × 25. The lower photomicrograph shows a section of a fourteen day human tibial graft. Living cells were found in the dense bone immediately adjacent to the deposits of new bone on the surface. In the intervening areas all lacunae were either empty or contained dead cells. Note the difference in structure of compact bone as compared to spongy bone (see upper photomicrograph). Reduced from a magnification of × 25.

In two of the specimens (one of each type of graft) a most interesting relationship was observed. As illustrated in figures 1, 2, 3 and 4 (rib graft), there were along the surface small areas of excessive deposits (compared to other specimens of the same age) of new bone separated by areas devoid of new bone. In the substance of the graft imme-

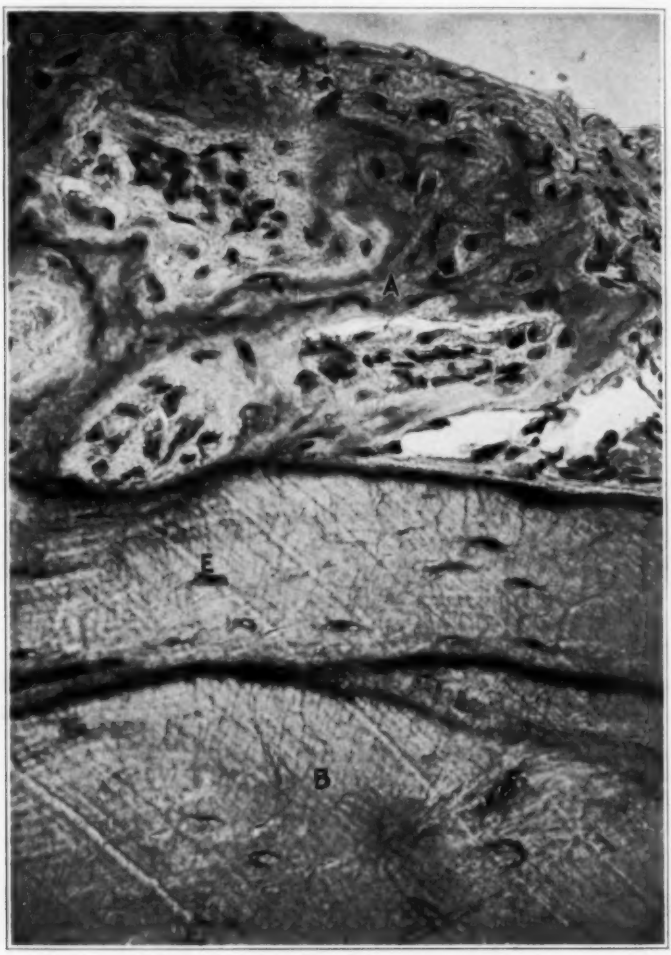

Fig. 2.—A higher magnification of the area marked *B'* in figure 1. The superficial living bone cells (*E*) stand out in sharp contrast to the dead cells in the deeper structure (*B*); the new bone (*A*) is deposited on the surface immediately over these cells. Reduced from a magnification of × 450.

diately underlying the trabeculi of new bone the lacunae contained living bone cells (figs. 2 and 3) which stood out in sharp contrast to the dead cells in the deeper structure and elsewhere along the surface (fig. 4), where there had been no new bone deposited. It is reasonable to assume

that this relationship of living transplanted bone cells to new bone formation is more than a coincidental occurrence. It speaks strongly for a function secretory or otherwise, inherent in osteoblasts and probably in other cells, which plays a constructive rôle in osteogenesis as opposed to the theory of a limited function of osteoclasis maintained by Leriche

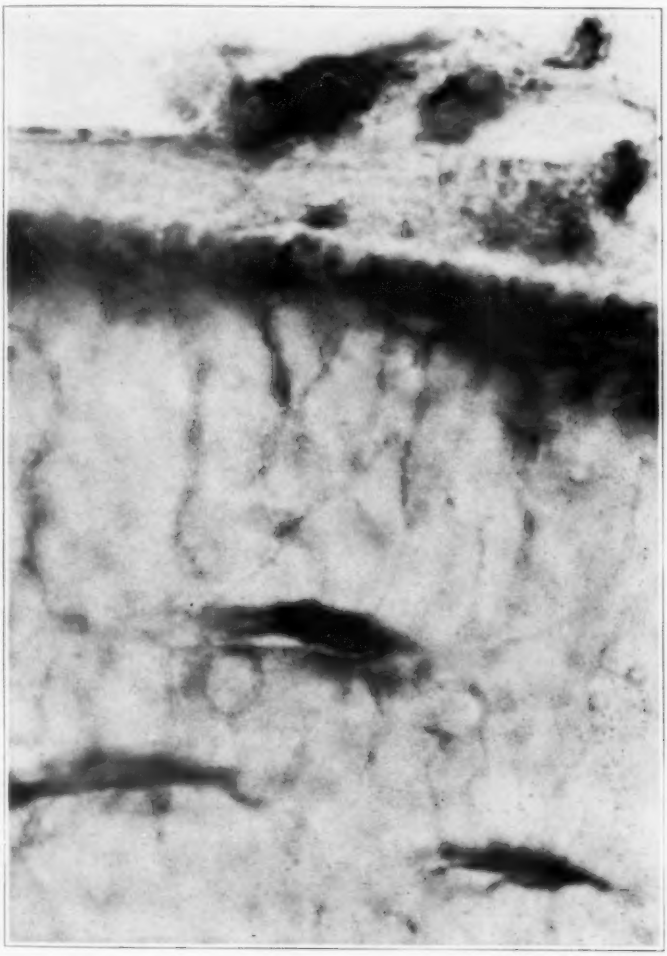

Fig. 3.—A higher magnification of the area labeled *E* in figure 2, to show living bone cells. Reduced from a magnification of × 2,600.

and Policard.[12] Despite encasement in bone, these cells presumably received sufficient nutrition to maintain cell life.

12. Leriche, R., and Policard, A.: The Normal and Pathological Physiology of Bone: Its Problems, translated by Sherwood Moore and J. Albert Key, St. Louis, C. V. Mosby Company, 1928.

The slowness with which dense bone undergoes absorption and replacement by new bone is illustrated in figure 5. This section was removed from a full thickness graft from the cortex of the tibia which had been transplanted seven months previously to effect an Albee type

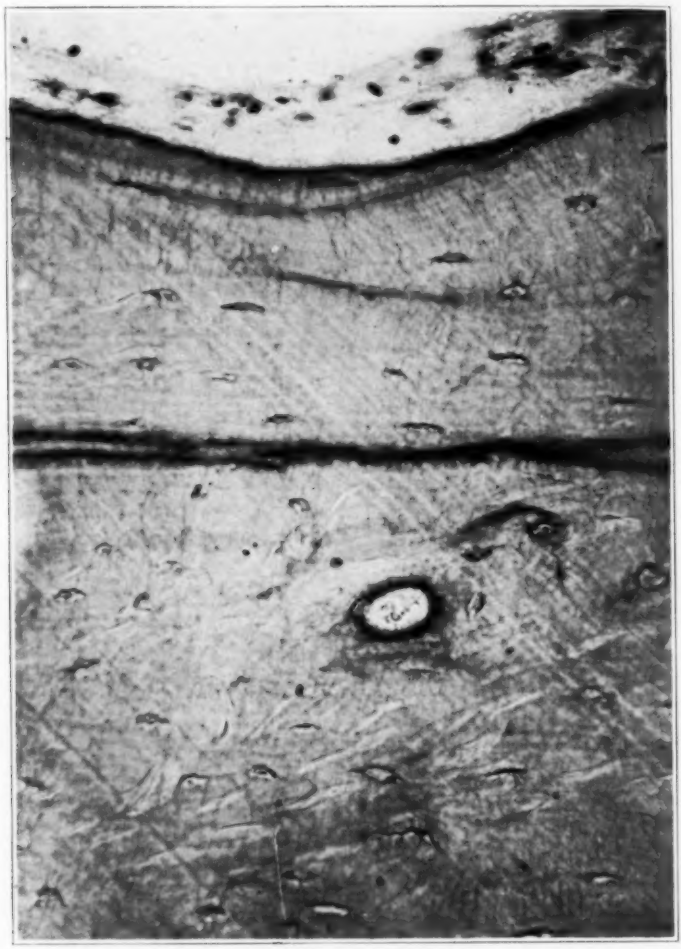

Fig. 4.—A higher magnification of the area labeled *X* in figure 1. All lacunae are either empty or contain dead cells. There was no new bone on the adjacent surface. Compare with figure 2. Reduced from a magnification of × 450.

of spinal fusion. Pseudo-arthrosis had developed in the graft near the middle of its span and necessitated a second fusion operation, at which time the specimen was obtained. It displayed all stages of the process

of creeping substitution (Barth [13] and Phemister [14]), extensive areas of dead bone, interspersed by areas of newly formed fibrous tissue and blood vessels and trabeculae of young new bone, while in other areas there was new bone undergoing reorganization and of an adult type. At the site of the pseudo-arthrosis there was no bone (old or new), and

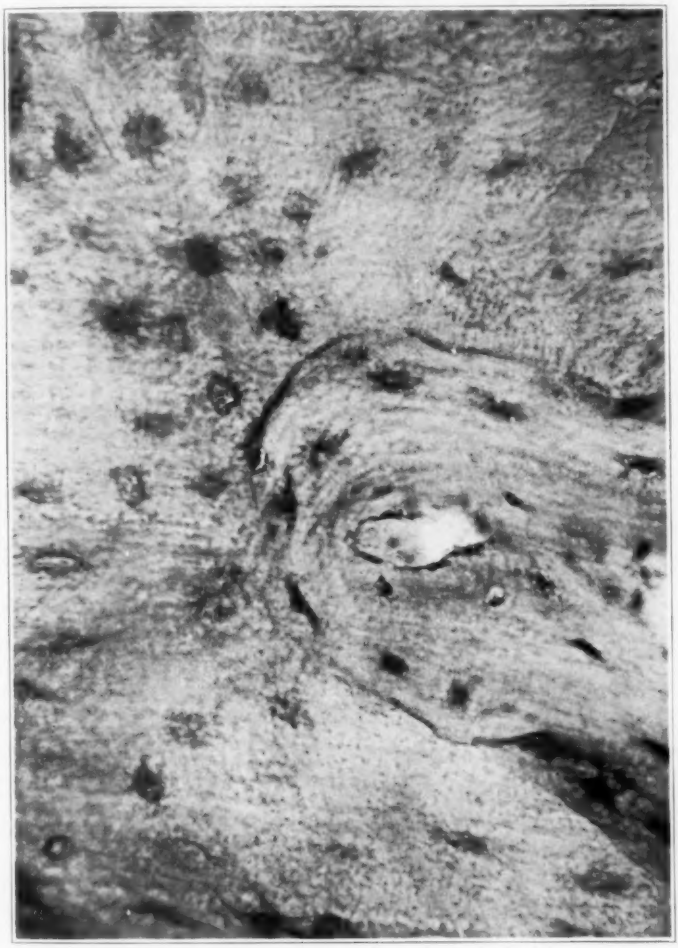

Fig. 5.—Well organized new bone laid down in necrotic bone following invasion of granulation tissue, revascularization and absorption in the process of creeping substitution. Note unreplaced necrotic bone of a human tibial graft seven months after transplantation to the spine. Reduced from a magnification of × 450.

13. Barth, A.: Histologische Untersuchungen über Knochenimplantationen, Beitr. z. path. Anat. u. z. allg. Path. **17**:65, 1895.

14. Phemister, D. B.: Necrotic Bone and the Subsequent Changes Which It Undergoes, J. A. M. A. **64**:211 (Jan. 16) 1915.

the space was filled with dense fibrous tissue. It appeared that replacement with new bone had failed to keep pace with the process of resorption.

EXPERIMENTAL FUSIONS

In thirteen half-grown kids, sections of ribs and tibiae were transplanted to beds of bone chips turned out from the laminae and against the denuded surfaces of the laminae. In all but four animals the spinous processes were removed and discarded. The grafts were of sufficient length to bridge three vertebrae and consisted of transplanted segments of ribs in six animals, full thickness tibial transplants with periosteum

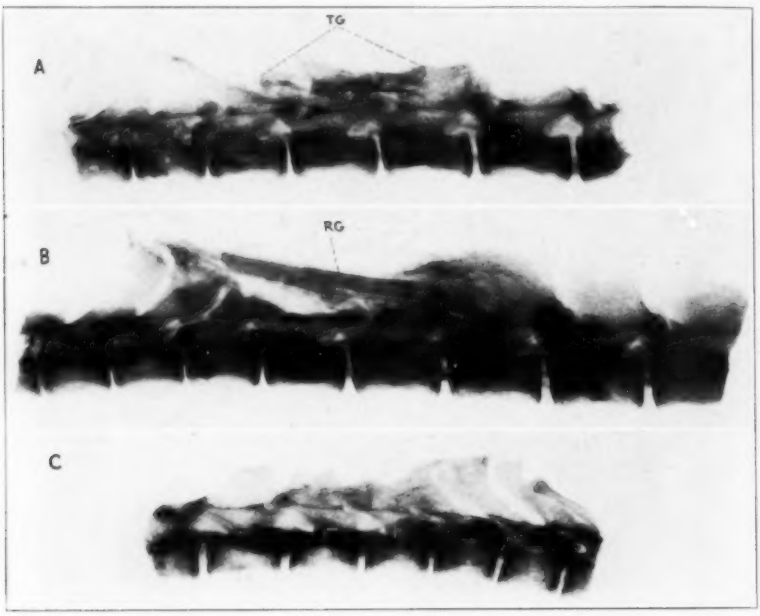

Fig. 6.—Roentgenograms of three spines ninety days after operation. *A*, a full thickness tibial graft. Note *TG*, unabsorbed necrotic bone of the transplant. *B*, infected rib grafts (*RG*), lying free in the abscess cavities; there was no invasion by granulation tissue; consequently there was a failure of absorption. The disastrous effect of a severe infection is well illustrated. *C*, a rib transplant entirely absorbed and replaced by new bone. Note the solid bony fusion.

in four animals and both rib and tibial grafts in three instances. No attempt was made to restrict the activities of the animals or to immobilize their spines after operation. They were killed at periods varying from seven days to five months, and microscopic sections from the areas in which the transplants had been placed were studied. In only one animal (fig. 6 *B*) was there a deep wound infection. In this instance the grafts acted as sequestrums floating free in the abscess cavities.

A chronological summary of the observations made in this group of experiments is as follows:

1. Three goats were killed seven days after operation. In one animal both tibial and rib grafts had been transplanted. The bone of all four transplants presented the usual appearance of necrosis. There was, however, considerable proliferation of the subperiosteal osteoblasts and of the cells on the endosteal surfaces of both tibial grafts and of one rib graft, which had been split longitudinally. On these surfaces there were also numerous capillaries with, in the split rib specimen, some invasion of the cancellous spaces.

In contradistinction to the tibial grafts, both rib transplants showed along the surfaces small areas of resorption with a few fine trabeculi of new bone.

2. Four similar specimens recovered from three animals at the end of two weeks revealed increased cellular proliferation with an ingrowth of capillaries in the formation of granulation tissue on all surfaces of the grafts. The tibial transplants presented the picture of beginning bone resorption and new bone formation as previously described and as observed in the rib grafts seven days earlier. The rib specimens displayed a more active and advanced stage of the same process. They were invaded rather extensively by granulation tissue, and definite deposits of new bone were in evidence.

3. Sections of each type of graft removed with the spines of two animals four weeks after transplantation revealed extensive absorption of the rib graft (fig. 7) with no increase in new bone as compared with that presented in the fourteen day specimens. The tibial transplant, however, had undergone much less absorption, but displayed about an equal amount of new bone. It appeared that at this stage in the rib specimen the process of absorption had greatly surpassed new bone replacement, whereas in the case of the tibial graft the two processes were more nearly keeping pace with each other.

4. In the comparative study of two sixty day specimens only small remnants of the dead rib could be discerned, and these were surrounded by an irregular mass of new bone which was continuous with that arising from the laminae. In contrast, the major portion of the tibial transplant remained unabsorbed, but likewise was surrounded by new bone which had established union with the laminae. The new bone laid down in and about the rib appeared to be greater in amount and somewhat more organized than that arising from the tibial transplant. This microscopic evidence of bony union and fusion was also demonstrable roentgenologically and by direct inspection.

5. Two animals were killed ninety days after operation. No vestige of the rib (fig. 6*C*) could be found in the sections studied, but in its

place was a large mass of new bone, much of which was organized into an adult type. It appeared that the major portion of the tibial graft had been absorbed and replaced by new bone, but considerable dead bone (fig. 6*A*) still remained in large irregular islands surrounded by

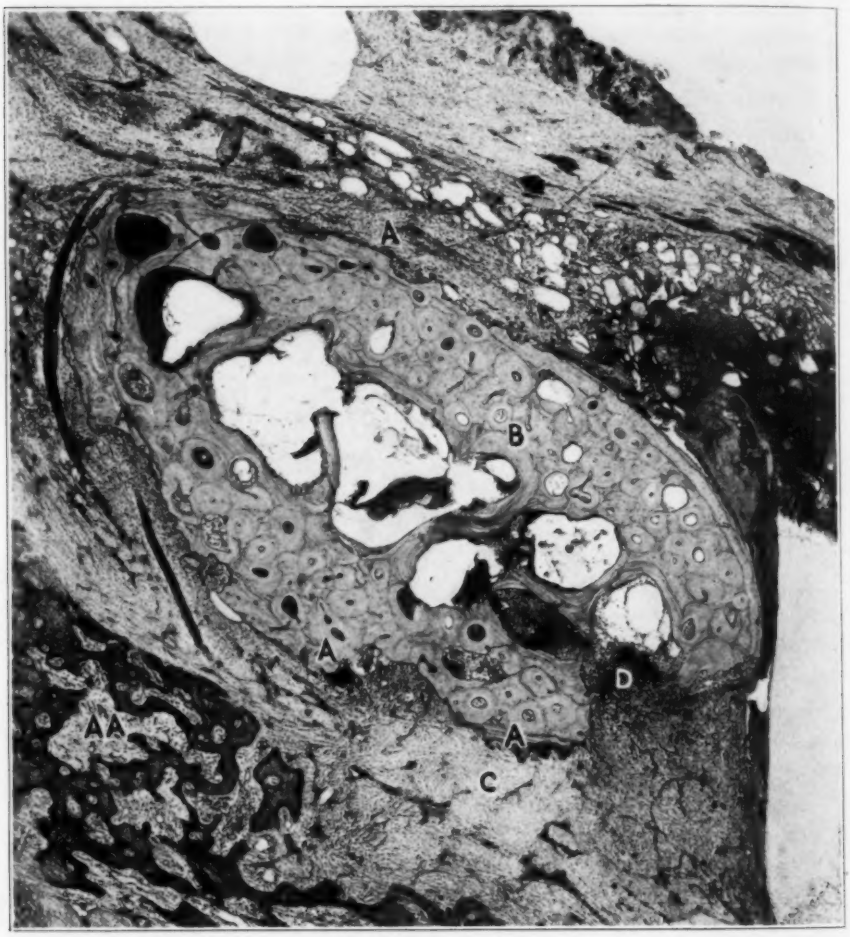

Fig. 7.—Rib graft thirty days after transplantation. The bone substance of the graft (*B*) is necrotic and undergoing rather extensive absorption and invasion by granulation tissue (*D*). There are numerous small deposits of new bone (*A*) and large areas of osteoid tissue with marked osteoblastic proliferation (*C*). The area (*AA*) represents new bone arising from the denuded surfaces of the laminae; × 30.

granulations and new bone. Bony fusion was apparent, as evidenced by continuity with new bone arising from the laminae.

6. One animal was killed one hundred and fifty-five days after operation and yielded two specimens for comparison. There were solid bony

fusion, no trace of dead bone of either the tibial or the rib graft and heavy deposits of new bone which were well organized and more dense than adult spongy bone.

In this series of experiments the bone, both dense and spongy, had without exception undergone necrosis. The cellular tissue on the surfaces and in open haversian canals and cancellous spaces of the trans-

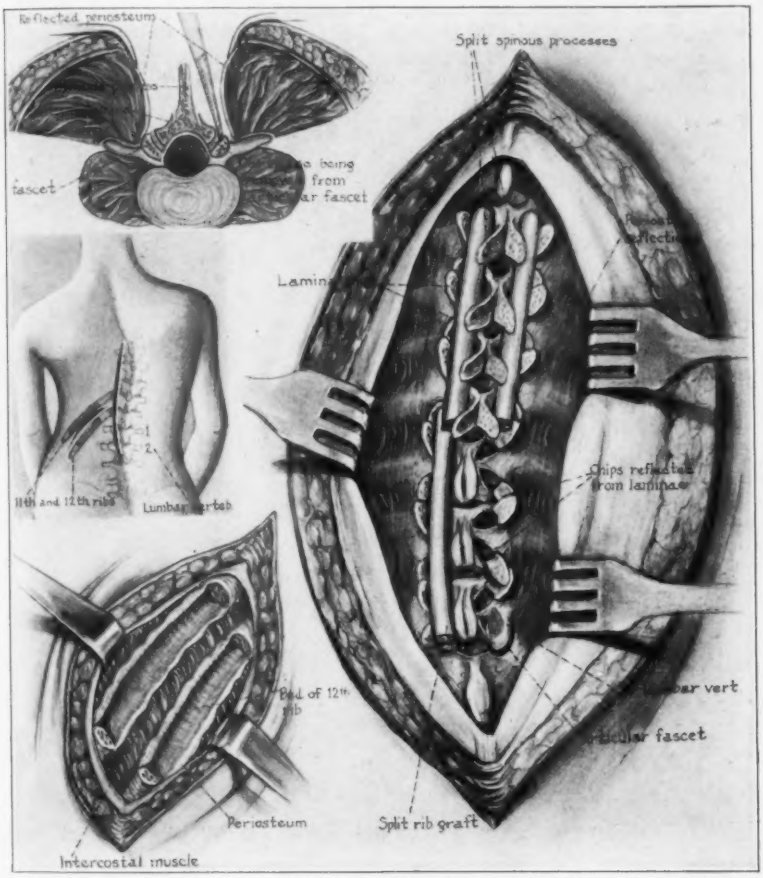

Fig. 8.—A modified Hibbs type of operation supplemented with rib grafts. The resected rib segments are split longitudinally and placed in the bed of overlapping fragments turned down from the laminae. The spinous processes are split and turned out over the transplants.

plants survived and within seven days showed considerable proliferation. The cells within lacunae, encased in bone, died and gradually disintegrated. The subsequent fate was that of absorption of the necrotic tissue and replacement by new bone. This process in the two types of

graft seems to differ only in respect to the influence played by the variance in architecture. Spongy bone (the rib) is much more cellular and much more porous. In consequence, it is presumably more permeable to nutrient bearing body fluids, and cellular proliferation occurs earlier and progresses more rapidly. For the same reason osteoclasis, invasion by granulation tissue and new bone formation appear earlier and up to a certain point advance more rapidly. Beyond this point resorption greatly exceeds replacement. In the dense bone of tibial transplants the two processes maintained a more nearly balanced equilibrium throughout.

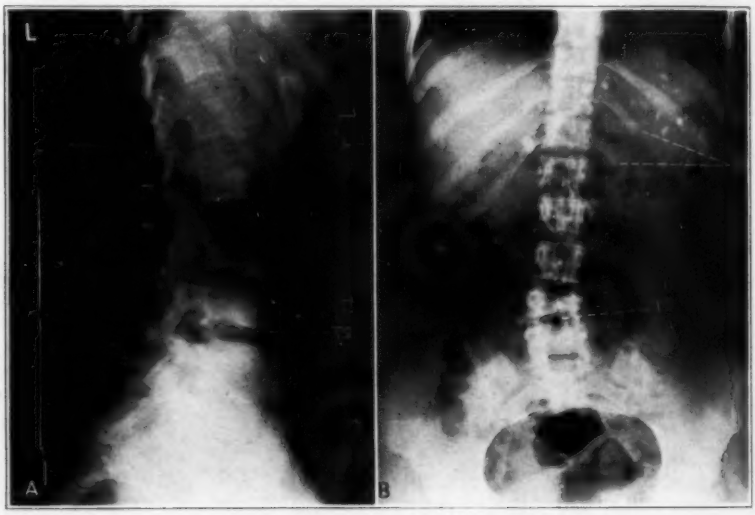

Fig. 9.—*A*, tuberculous spondylitis (*TS*) involving the bodies of the fourth and fifth lumbar segments. *RG* represents the span of fusion and rib grafts; *NB*, new bone deposit. *B*, note the calcified tuberculous lymph nodes and foci in the region of the spleen. *RB* indicates stumps of resected rib segments.

CASE REPORTS

The subsequent clinical deductions are based on a study in which rib grafts were transplanted to the spine, as illustrated in figure 8. This operation differs from that described by Allison [15] only in the use of rib grafts in place of osteoperiosteal transplants from the tibia, and from that referred to by Kleinberg [6] in the immediate transplantation of fresh grafts. It is essentially the Hibbs operation, with the additional support, the impetus to osteogenesis and the greater surety of a massive firm fusion to be gained from the engrafting of bone.

15. Allison, N.: Fusion of the Spinal Column, Surg., Gynec. & Obst. **46**:826, 1928.

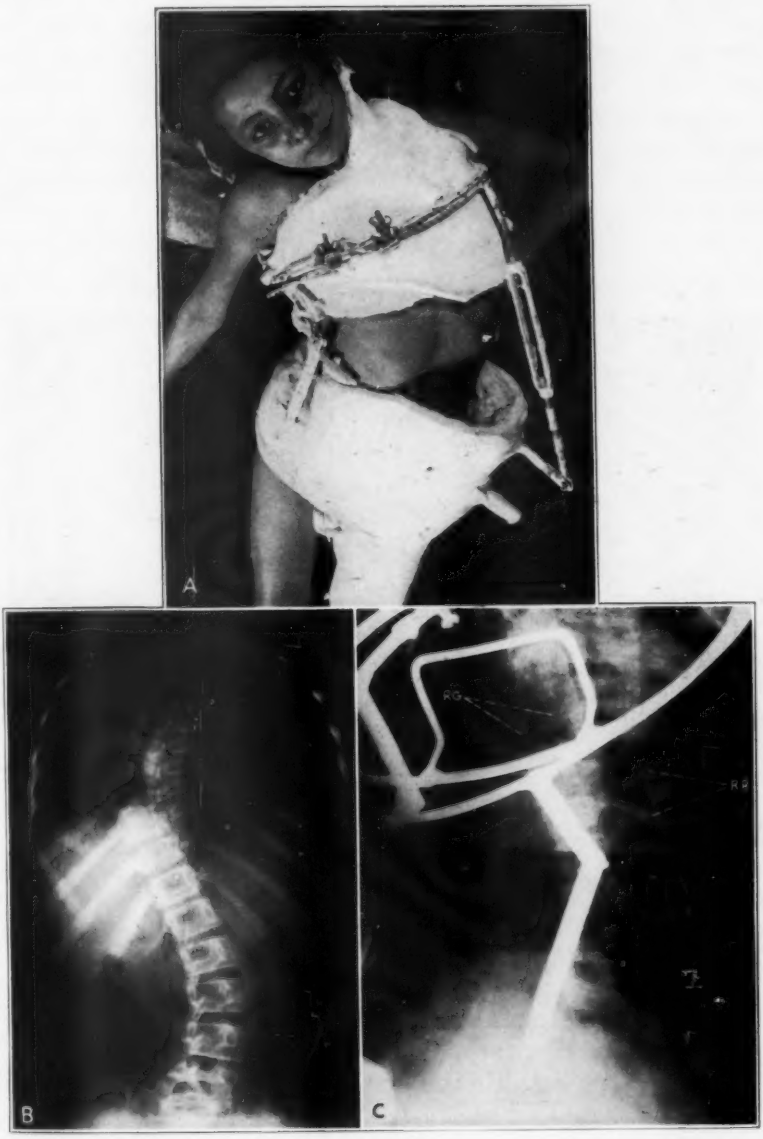

Fig. 10.—*A*, a patient with idiopathic scoliosis receiving correction of the spinal curvature in a modified (Risser), hinged, turnbuckle jacket. *B*, roentgenogram of the spine of the patient in *A* before correction and fusion. *C*, roentgenogram of the same patient after correction and the second stage of spinal fusion. *RG* points to rib grafts and *RR* to stumps of resected rib segments (the tenth and eleventh segments). Turnbuckle correction was continued after operation. Note the almost complete correction of the spinal curvature.

The ages of the twelve patients varied from 2 to 24 years, and the areas of the spine fused ranged from the sacrum to the second thoracic vertebra, inclusive. The group was composed of four cases of vertebral tuberculosis (figs. 9 to 12) and eight cases of scoliosis (figs. 10 *A* and *B* and 11 *A*). The latter series may be subdivided in regard to etiology into idiopathic, three cases; ricketic, one case; paralytic (anterior poliomyelitis), two cases, and congenital vertebral deformation, two cases. The two patients with congenital deformities of the spine were operated on by Dr. Compere,[16] and the fusion operations were supplemented by the removal of deformed vertebral bodies (two in one of the cases and one in the other).

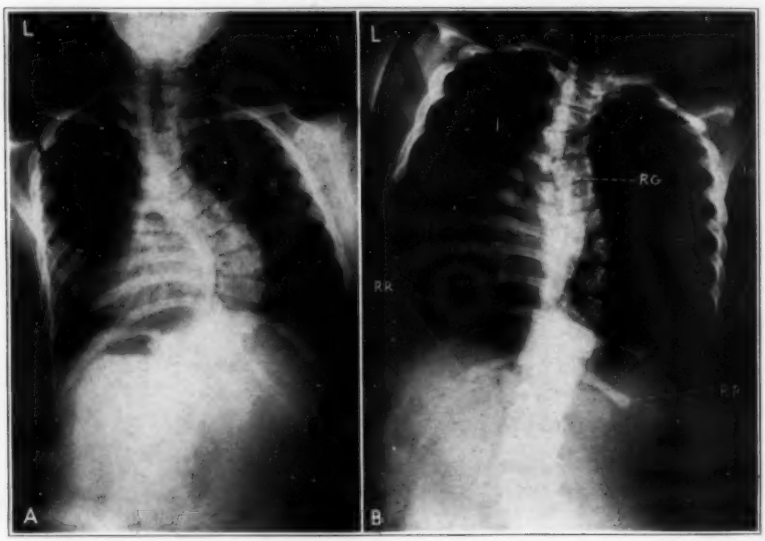

Fig. 11.—*A*, ricketic scoliosis before correction and fusion. *B*, after correction and spinal fusion in two stages. *RG* points to shadow of rib graft and *RR* to stumps of resected rib segments. Note the regeneration of the ribs on the left side and the marked correction of the curvature.

The rib transplants consisted of segments from 14 to 22 cm. in length removed from two or more ribs, in most instances from the tenth and eleventh or from the eleventh and twelfth. In one case of scoliosis with a rather marked posterior bulge of the thoracic cage, the rib segments were resected from the center of that area to decrease the deformity by flattening the bulge.

In all cases a solid bony fusion was demonstrable clinically and by roentgen examination within three months after operation.

16. Compere, E. L.: Excision of Hemivertebrae for Correction of Congenital Scoliosis, J. Bone & Joint Surg. **14**:555 (July) 1932.

The advantages of rib grafts for general use have been outlined by Eloesser:

1. No special instrumentarium such as a motor-driven saw is required.

2. The rib is more workable than dense cortical bone; it can be bent and cut more readily.

3. The supply is practically unlimited, and the removal of segments of two or three ribs does not affect the well-being of the patient.

Fig. 12.—Extensive vertebral tuberculosis. Note the shadows of the rib transplants. *RR* marks the extent of fusion and of grafts.

4. The rib resection is neither more difficult nor more dangerous (with due caution to avoid injury to the pleura), nor does it require more time than the removal of a graft from the tibia.

In respect to their use for spinal implantation, the following advantages may be added:

1. The grafts are accessible in the same general field of operation.

2. The curve of the rib at its angle frequently is well adapted to the contour of the spine in cases of kyphosis or scoliosis.

3. There appears to be less shock than that associated with the removal of a tibial graft.

4. The grafts offer an alternative in certain cases in which tibial grafts are not available, owing to associated infection or fractures of the tibiae or loss of the lower extremities, or under circumstances in which a scar of the leg would be greatly objected to.

5. As described by Whitman, the resection of ribs may serve a dual function in cases of scoliosis with rotation deformities of the chest.

SUMMARY AND CONCLUSIONS

1. Both clinical and experimental comparative studies of costal and tibial bone grafts are reported. These studies relate particularly to quantitative osteogenesis of the two types of bone represented, with reference to clinical application in spinal fusion operations. Ribs undergo revascularization and absorption and are replaced by new bone much more rapidly and extensively than dense bone. When no great demand is made on the inherent strength of the graft, as in the type of operation illustrated, ribs serve the purpose of transplanted bone as satisfactorily as do full thickness tibial grafts and probably more effectively than thin osteoperiosteal transplants. Likewise, certain advantages of minor significance are pointed out.

2. Some evidence in support of the cellular theory of osteogenesis is presented. That all transplanted bone does not die is demonstrated by the survival of cells in lacunae encased in bone in two of the six specimens from human beings recovered twelve and fourteen days, respectively, after transplantation. The early and heavy deposits of new bone on the surface overlying these living bone cells suggest a definite osteogenic interrelationship.

LYMPHOBLASTOMAS OF THE GASTRO-INTESTINAL TRACT

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Lymphoid tumors of the gastro-intestinal tract are by no means rare and have been treated at length in the literature of the past three decades. The majority have been included in the more or less general term of sarcoma, but while such a classification is no doubt correct, the lymphoid tumors form a group in themselves and should be considered separately. The histogenesis of this group is still marked by obscurity and has been the basis for much controversial opinion. The nomenclature is confused, and owing to a lack of knowledge of the histogenesis of these tumors, they have run the gamut of pathologic classification.

More important than a suitable nomenclature is the recognition of a malignant process. Some of the tumors undoubtedly are malignant. They metastasize and recur after excision. Others pursue the course of a benign growth, and it is frequently impossible to differentiate the two types microscopically.

The problem confronting the pathologist is twofold, first to form a suitable working classification and second to recognize the grade of malignancy. For this purpose a study has been made of 45 cases occurring in the Surgical Pathological Laboratory of the Johns Hopkins Hospital.

HISTORICAL DATA

Most of the literature on intestinal sarcomas has appeared during the past forty years. In 1883, Debrunner [1] described one of the earliest authentic cases occurring in the large bowel. Pick's [2] case was reported the following year. Pitt [3] was able, in 1889, to gather reports of 18 cases from the literature and added 1 case of his own, but he classified them all as lymphadenomas. Orth,[4] in an inaugural thesis, one year later, gave abstracts of 11 cases of sarcoma of the intestines, which were about evenly distributed between the small intestine, the colon and

From the Surgical Pathological Laboratory, Department of Surgery of the Johns Hopkins Hospital and University.

1. Debrunner, A.: Inaug. Diss., Zurich, 1883.
2. Pick, E.: Prag. med. Wchnschr. **9**:96, 1884.
3. Pitt, G. N.: Tr. Path. Soc., London **40**:80, 1889; Rev. gén. de clin. et de thérap. **44**:380, 1930.
4. Orth, L.: Inaug. Diss., Heidelberg, 1890.

the rectum. Baltzer's [5] comprehensive review of the subject appeared in 1892. He covered the subject in detail and commented on the predilection of lymphoid tumors for the small intestine. Libman's [6] article published in 1900 was no doubt the best review to that date and contained a list of all cases reported to that time, totaling 59. Crowther [7] reviewed the literature again in 1913 and compiled statistics on 122 cases. In 1919, Graves [8] extended this number to 249.[9] The work of Liu,[10] published from this laboratory, while brief, is the latest comprehensive survey.

Although lymphoid tumors have been the object of much discussion, most pathologists admit an inadequacy of knowledge dealing with classification, diagnosis, pathogenesis and prognosis. As a result, most of the cases are reported in the literature under a variety of names. Sarcoma is perhaps an all inclusive term; certainly most of this group of tumors have fallen originally into that classification. The name implies a definite malignant process, however, and cannot be applied to certain tumors which show no malignant characteristics. Neither can the name infectious granuloma or chronic inflammatory tumor be applied with impunity to a tumor every feature of which supports the impression of a high grade of malignancy. Graves, noting its ambiguity, made a plea for uniformity of nomenclature. He suggested the term lymphoblastoma, which, according to Mallory,[11] means "a tumor of mesenchymal origin, the cells of which would normally tend to differentiate into cells of the lymphocytic series." Such terms as "round cell sarcoma" are no doubt correct, but indicate little more than the morphology of the cells. The name "chronic inflammatory tumor" tells nothing of the morphology and is misleading from the standpoint of histogenesis. Considering the group in its various phases, it has seemed preferable to adopt Graves' term for the purpose of unification.

LOCATION

In view of the increasing number of cases appearing in the literature, it would be a difficult task to attempt a summary of all reported cases of lymphoblastomas of the gastro-intestinal tract. The 45 cases occur-

5. Baltzer, A.: Arch. f. klin. Chir. **44**:717, 1892.

6. Libman, E.: Am. J. M. Sc. **120**:309, 1900; **129**:813, 1905.

7. Crowther, C.: Clin. chir. **21**:2107, 1913.

8. Graves, S.: J. M. Research **40**:415, 1919.

9. These reports include only tumors of the small intestine and ileocecal region, and exclude those of the stomach and large intestine.

10. Liu, J. H.: Tumors of the Small Intestine with Especial Reference to the Lymphoid Cell Tumors, Arch. Surg. **11**:602 (Oct.) 1925.

11. Mallory, F. B.: The Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914; J. M. Research **13**:113, 1904-1905; J. Exper. Med. **10**:575, 1908.

ring in this laboratory form a composite group and are used as a basis for study of the characteristic features of the tumor. These cases are representative of the distribution throughout the tract (table 1).

Lymphoblastomas apparently have a predilection for the stomach, small intestine and colon. Of these, the smaller intestine is the most frequent site, and of its subdivisions, the terminal part of the ileum is by far the most common seat of the lesions. No tumors were found in the appendix or the jejunum. Although not specified in table 1, the ileocecal region contained the majority of tumors in the ileum and colon.

AGE, SEX AND RACE INCIDENCE

It is interesting to note that the majority of investigators have commented on the occurrence of lymphoblastomas in young people. The same is more or less true of all sarcomas, but especially so in this type

TABLE 1.—*Distribution of Forty-Five Lymphoblastomas*

Location	Number of Cases
Stomach	13
Duodenum	1
Jejunum	0
Ileum	19
Appendix	0
Colon	11
Rectum	1
Total	45

of tumor. The youngest patient of this series was only 6 months old; the oldest was 77 years. The average age was 41 years. Attention should be called to the fact that the age curve (fig. 1) reaches two peaks, one in the first decade and a second, higher peak in the fifth decade. If one next analyzes the curves for the different parts of the intestinal tract, another surprising difference is found. Gastric lymphoblastomas occur with greatest frequency between the ages of 50 and 60, with no cases at a younger age. The peaks of frequency in the small intestine, on the other hand, fall in the second and fourth decades, after which the curve drops gradually to the eighth decade. The curve for the colon and rectum combined follows in general the curve of all cases.

The ratio between the sexes is roughly 2 to 1, with a predominance in males. This corresponds to the ratio of all gastro-intestinal cancer and is not significant. Negroes are affected only one-seventh as frequently as white persons, but this likewise is not a significant observation, since the latter come under medical observation much more frequently than do Negroes.

CLINICAL OBSERVATIONS

The clinical manifestations of lymphoblastomas are not unlike those brought on by any malignant process in the gastro-intestinal tract.

The general symptoms are malaise, cachexia, loss of weight, weakness and secondary anemia. Some authors point out the greater severity of these symptoms in lymphoblastoma than in carcinoma and attempt to differentiate the two conditions on this basis. Attention was called to the absence or late appearance of obstruction by Treves and Baltzer.[5] This is regarded as a diagnostic point by Williams,[12] Haggard [13] and others. While it is true that general symptoms are usually present before obstruction develops, this fact cannot be regarded as an infallible sign in view of its inconstancy in lymphoblastomas and its occasional occurrence in carcinomas. Pain is a fairly constant symptom, but is of

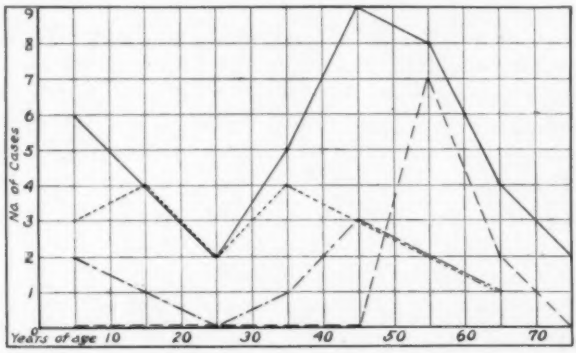

Fig. 1.—Graph representing the age incidence for tumors in various parts of the gastro-intestinal tract. The solid line represents the entire group; the dash line, the stomach; the dot line, the small intestine, and the dash and dot line, the large intestine. Note the difference between the age incidence for tumors occurring in the small intestine and that for those occurring in the stomach.

a dull, aching type in contradistinction to the sharp and cutting variety characteristic of acute obstruction. Even this, however, is frequently delayed for some time after the beginning of the tumor, and on account of the absence of symptoms, the tumor may go unrecognized for months.

Nausea and vomiting are usually present at some time in the course of the disease, but are not marked, and the clinician may be at a loss to explain their presence in the absence of other indicative signs. Distention rarely occurs early in the disease, but the patient may complain of vague abdominal distress and attacks of indigestion.

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12. Williams, E. M.: New Orleans M. & S. J. **66**:173, 1913-1914.

13. Haggard, W. D.: Tumors of the Small Intestine, J. A. M. A. **59**:253 (July 27) 1912.

There is nothing characteristic about the stools. Some patients complain of marked constipation; others, of diarrhea, but more commonly of alternating attacks of constipation and diarrhea. Melena is not a frequent occurence.

Laboratory findings reveal varying degrees of secondary anemia and a moderate leukocytosis. The stools may or may not contain occult blood.

A slight rise in temperature in the afternoon (from 99 to 100 F.) is a more or less constant feature and is partially responsible for the infectious theory of the origin of the tumor. The presence of fever with sarcoma has been recognized for several years, and many early papers call attention to it as distinctive. Williams [12] suggested the resorption of a toxic material from necrotic areas as a possible explanation, but this theory is without proof. An indirect effect of the tumor on the body metabolism is more plausible.

Roentgen findings may show a filling defect in the stomach or the large intestine or a dilatation of the proximal bowel if obstruction is present. If the tumor is in the small bowel, roentgenograms are of less value, owing to the difficulties of localization and of obtaining a homogeneous distribution of barium throughout the intestine. In rare instances, a bulbous shadow may be present owing to the dilated form of the tumor. When negative, the roentgen findings do not rule out a tumor, and when positive, it is impossible to localize in the majority of cases.

Intussusception is a frequent complicating condition and is responsible for a characteristic clinical syndrome. The onset is marked by the acute pain of intestinal obstruction with vomiting, distention, tympanites and obstipation. A sausage-shaped tumor is frequently palpated, usually in one or the other flank. A few bowel movements containing bloody mucus may occur immediately following the intussusception, but soon cease altogether. The condition is symptomatically identical with the spontaneous intussusception occurring in infants, but does not reduce itself. Kasemeyer [14] stated that 10 per cent of 284 cases of intussusception reviewed by him were caused by sarcomas. The condition is frequently found at the ileocecal valve, resulting in an ileocolic invagination, and is due partly to the ease with which this part of the bowel invaginates, and partly to the frequency of lymphoblastomas in this region.

DIAGNOSIS FROM CARCINOMA

While it is not attempted to differentiate lymphoblastomas from carcinomas on the bases of clinical data alone, the characteristic features

14. Kasemeyer, E.: Deutsche Ztschr. f. Chir. **118**:205, 1912.

of each as derived from personal observation and from the literature are as follows:

	Lymphoblastoma	Carcinoma
Age:	Young. Patients are usually in first four decades. May occur in infants	Attacks persons of the "cancer age" in the fifth and sixth decades
Location:	Most common in lower part of the ileum and cecum	Most common in stomach and rectum
Course of Disease:	Rapid	Prolonged
Pain:	Dull and aching, occurring late in disease	Sharp and cutting following distention and coincident obstruction
Obstruction:	Occurs late or not at all	Commonly found
Laboratory Findings:	Blood in stools rare. Rise in temperature in afternoon present. Anemia severe	Blood in stools common. Rise in temperature in afternoon absent. Anemia moderate
Gross Form:	Large aneurysmal dilatation	Small annular constriction

These differences should be accepted with reservation, since probably no one tumor will show all of the characteristics. Nevertheless, when a majority are present, they may be extremely useful in differentiating the two conditions.

GROSS PATHOLOGIC CHANGES

Occurring so often that they cannot be considered accidental, lymphoblastomas produce dilatation rather than constriction of the intestine. This characteristic has drawn the comment of many investigators. Williams,[12] Jopson and White,[15] Nothnagel[16] and others regarded it as typical. A popular explanation of the phenomenon is the invasion of the muscular coats with paralysis and subsequent dilatation. Another theory is that of origin in the submucosa followed by subsequent infiltration and extension through the planes of least resistance. The tumor frequently resembles a hollow sphere with a moderate degree of constriction at either end, where the lumen of the intestine enters and leaves the tumor (fig. 2). This, however, occurs chiefly in the small intestine. In the stomach and large bowel the form is more apt to be pedunculated or sessile (figs. 3 and 4). Fletcher[17] described a case with multiple plaques arising from the aggregate nodules in the terminal ileum. Brettauer's[18] patient had multiple hard white nodules in the cecum.

The tumor is white, and its consistency is firm and rubbery. The cut section has a translucent sheen. The mucosa is usually intact over the tumor unless the tumor growth has impaired the circulation and caused devitalization. Areas of central necrosis are sometimes seen, and sterile, purulent fluid with necrotic tumor tissue is evacuated. The

15. Jopson, J. H., and White, C. Y.: Am. J. M. Sc. **122**:807 1901.

16. Nothnagel, H.: Diseases of the Intestines and Peritoneum, Philadelphia, W. B. Saunders Company, 1904, p. 460.

17. Fletcher, W.: Practitioner **83**:374, 1909.

18. Brettauer, Joseph: Am. J. Obst. & Gynec. **76**:90, 1917.

Fig. 2.—Gross photograph of a lymphoblastoma of the ileum, illustrating the typical aneurysmal dilatation characteristic of lymphoblastoma (Path. no. 41291). The tumor surrounded the lumen of the intestine and produced a dilatation, rather than the stenosis characteristic of carcinoma. This was a malignant reticuloma. It was removed at operation, but the patient died three months later of metastases.

Fig. 3.—Photograph of a section through a polypoid lymphoblastoma (Path. no. 16485). This was one of six polyps occurring in the upper part of the jejunum. It had produced an intussusception. The intussuscepted bowel was removed at operation together with a portion of the bowel containing the remaining tumors. Convalescence was uneventful, and the patient is entirely well. This was a malignant lymphocytoma.

fluid may be so predominant at times as to cause the tumor to be mistaken for an abscess.

The size varies greatly. As a rule, on account of the peculiar form of the aneurysmal dilatation, the tumors attain a much larger size than carcinomas, and it is not at all uncommon to see a tumor the size of a grapefruit.

MICROSCOPIC PATHOLOGIC CHANGES

The histologic anatomy of the lymphoblastomas is typified by dense accumulations of closely packed cells with a stroma of varying abundance. The tumor is usually located in the submucosa and does not involve the mucosa which passes intact over the surface. The direction assumed by the tumor in its growth is usually parallel to the intestine. It seeks the planes of least resistance, and produces a flattened tumor. In advanced stages, especially of tumors of a malignant

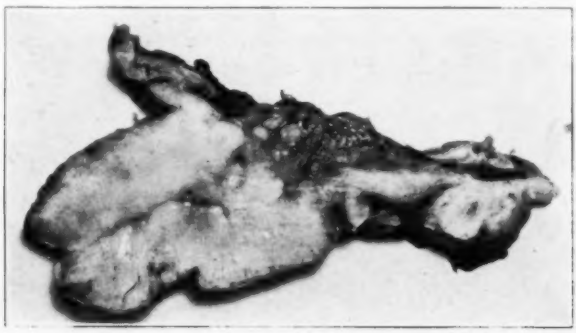

Fig. 4.—Photograph of a pedunculated lymphoblastoma arising in the cecum near the ileocecal valve (Path. no. 29605). It had produced an ileocolic intussusception. The right half of the colon was removed, and a lateral ileocolostomy was performed. This was a malignant lymphocytoma. The patient recovered and is well.

nature, the muscularis is invaded or infiltrated. In some instances the vascularity is increased, but in the majority it is impaired and the vessel walls are invaded by the tumor. An admixture of leukocytes, plasma cells and mononuclear cells is commonly seen. There is a surprising predominance of eosinophils. The tumor cells themselves vary somewhat with the type most commonly found in the intestinal tract.

Benign Lymphocytoma.—This is the benign type of tumor commonly thought to be of infectious origin, but the etiology of which is sometimes obscure. The cells comprising the tumor are of the small, lymphocytic variety (fig. 5). They are round and contain a dark-staining nucleus and a minimal amount of cytoplasm. They are not dispersed homogeneously throughout the tumor, but may be sparse in some parts and densely packed in others. The extension of the tumor is of a benign nature, the cells infiltrating between the normal elements without giving

the picture of malignant destruction. Plasma cells may be abundant. The stroma is scant in some places, but in others there may be a dense fibrous reaction with hypertrophy of the connective tissue. When this fibrosis is marked and large giant cells of the Dorothy Reid type are present, it is suggestive of intestinal Hodgkin's disease, although the occurrence of this entity is still a matter of doubt. If the cells have a

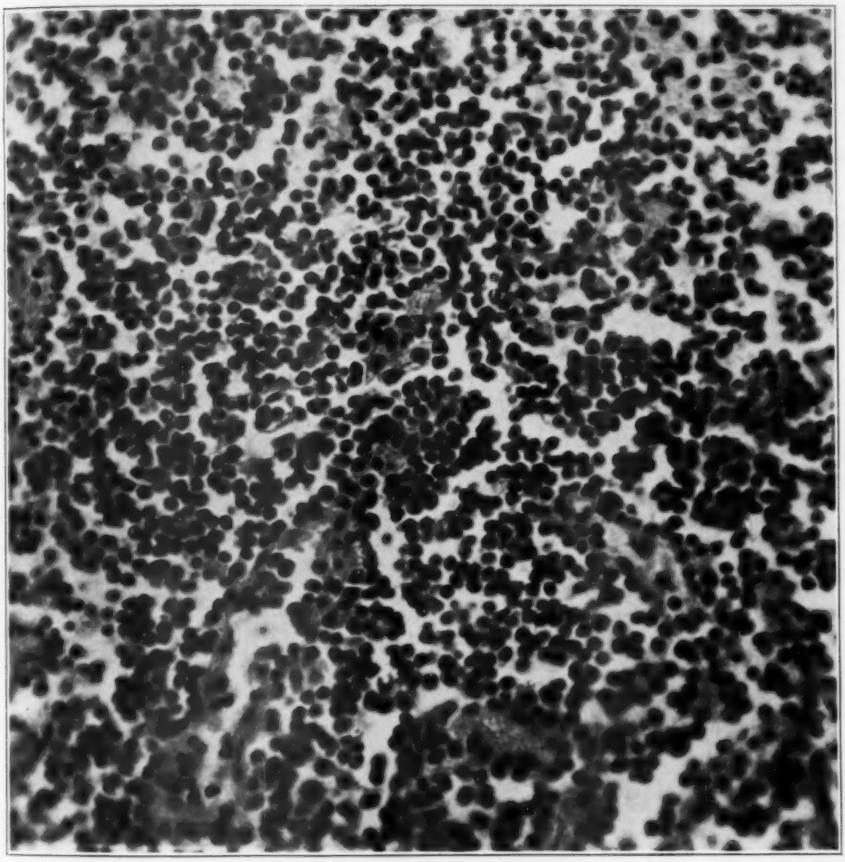

Fig. 5.—Low power photomicrograph of a nonspecific granuloma in the stomach (Path. no. 44757). Note the uniformity of size of the lymphocytic cells, the absence of reticulum and the irregular disposition of the cells between the stroma of the wall of the stomach.

predilection for perivascular arrangement, syphilis may be suspected. The presence of tubercles and characteristic giant cells is indicative of tuberculosis. Occasionally the intestinal tumor may be part of a generalized process such as lymphatic leukemia. When none of these characteristics are present, the tumor is left in the rather loose classi-

fication of nonspecific granuloma, comprising a heterogeneous group sometimes indistinguishable from tumors of a malignant nature.

Malignant Lymphocytoma.—This group of lymphoblastomas differs from the preceding both in the character of its cells and in the

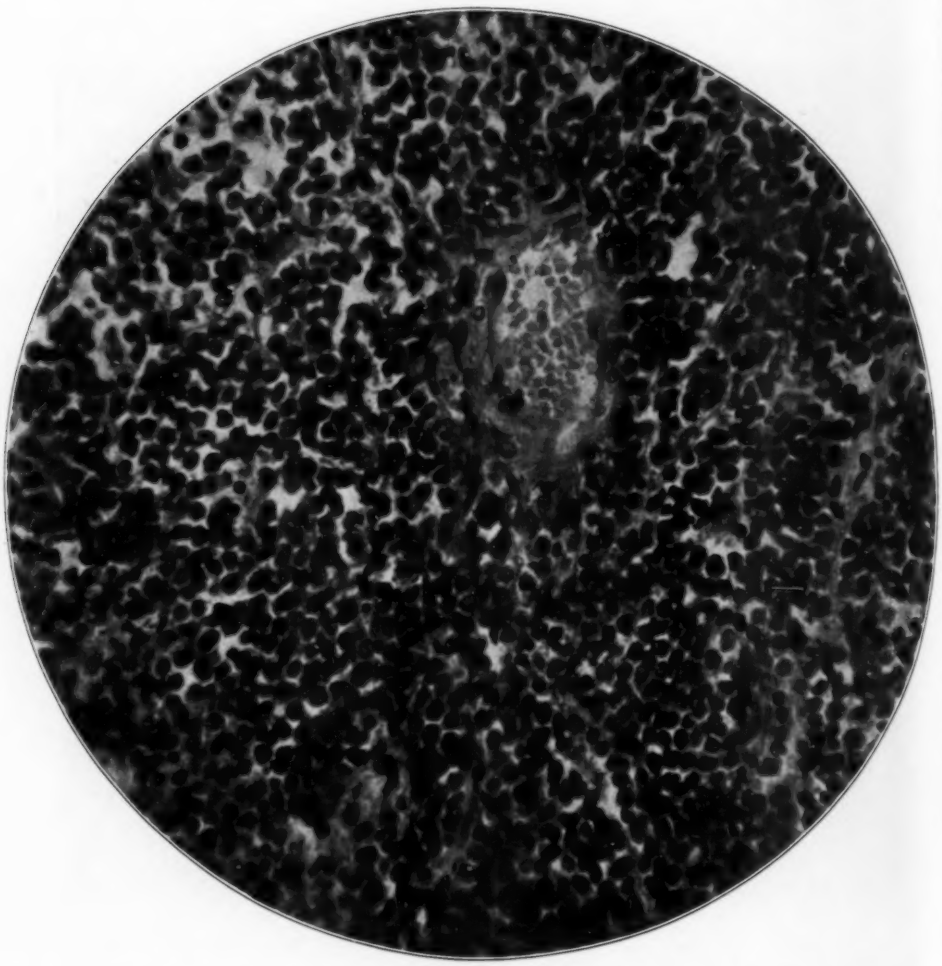

Fig. 6.—Low power photomicrograph of the tumor shown in figure 4 (Path. no. 29605). Note the closely packed accumulations of round cells, which are larger than normal lymphocytes. They are invading the tissue profusely, but have not encroached on the lumen of the blood vessel in the center of the picture.

manner of its growth. The majority of the cells are slightly larger than normal lymphocytes. They are uniformly round, with scanty cytoplasm. The nucleus stains much lighter and contains numerous chromatin particles which have a tendency toward central arrangement.

One or more nucleoli may be seen (fig. 8). Cells resembling normal lymphocytes may also be present, and between these two forms, one may find cells representing all stages of transition from normal lymphocytes to tumor cells.

The tumor cells are packed closely together and form a dense homogeneous mass which does not, however, destroy the normal archi-

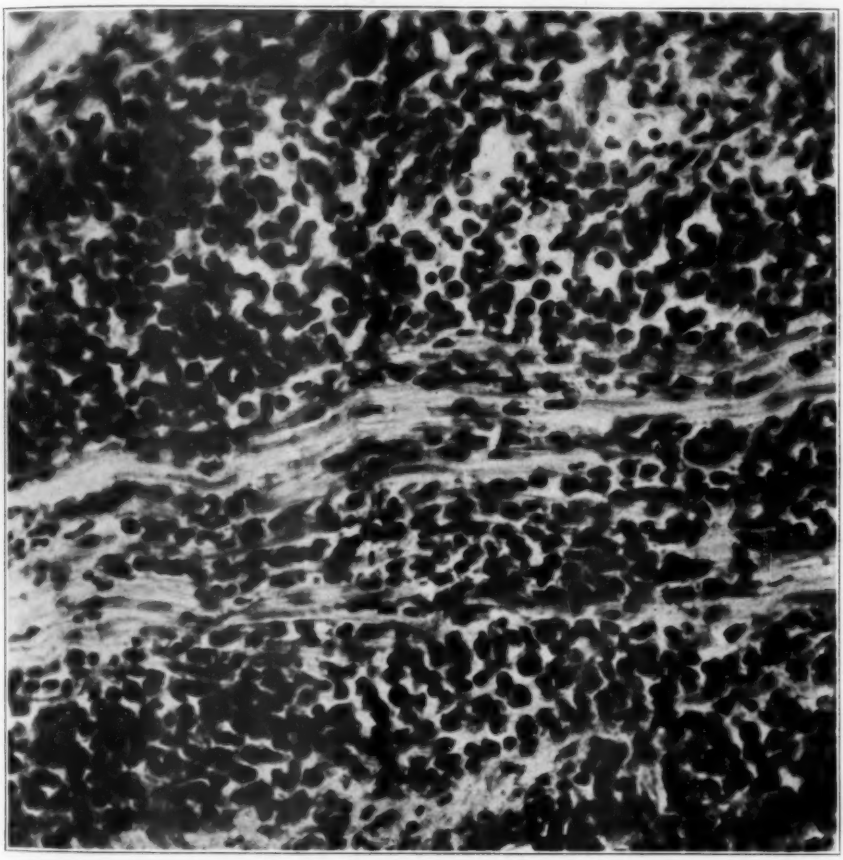

Fig. 7.—Low power photomicrograph of a malignant lymphocytoma of the colon (Path. no. 28312). The cells are similar to those described in the preceding photograph and are infiltrating between the connective tissue fibers of the intestinal wall without destroying them.

tecture of the intestinal wall (fig. 7). Instead, they are packed between the muscle and connective tissue fibers and apparently follow the lines of least resistance. Vascularity is not marked, and the capillaries present are not invaded by the tumor cell (fig. 6).

Giant cells are rarely if ever seen. Eosinophils are common, and small plasma cells are abundant.

Benign Reticuloma.—This type is not a true tumor formation, but is analogous to the hyperplastic lymphadenitis common in the presence of either an infectious process or a malignant condition of the bowel. It typifies the enlarged, hard mesenteric gland frequently mistaken at operation for metastatic carcinoma.

On section one finds not the malignant cells of the neoplasm, but a hyperplasia of the reticulum cells of the primordial follicles and lymph sinuses (fig. 9). The cells are large and polygonal and possess a moderate amount of cytoplasm and a dark-staining nucleus. There are

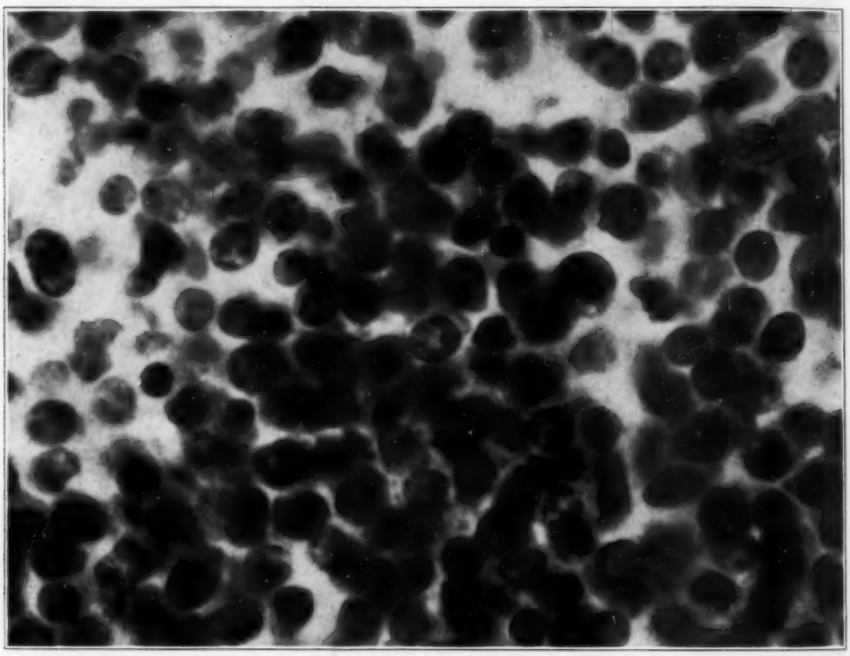

Fig. 8.—High power photomicrograph of a malignant lymphocytoma of the colon (Path. no. 28312). (From the same case as fig. 7.) Note the regularity of the cell structure both in size and in staining reaction. There are smaller cells which are normal lymphocytes between this type and the larger cells. All stages of transitional growth may be observed.

many other cells resembling endothelial cells which are larger and take a lighter stain, the nuclei of which contain numerous chromatin particles. Reticulum is abundant and forms a loose, supporting stroma for the cells. This is apparently a normal stimulatory response, and while it perhaps has no place in a consideration of neoplastic growth, it should be included as the benign counterpart of the malignant reticuloma in the following group.

Malignant Reticuloma.—These are the tumors thought to arise from the reticulum cells of the primordial follicles of the lymph nodes. The

cells are large and show an active state of proliferation (fig. 10). The nuclei are large and round or oval, and contain a large number of chromatin particles, which are most frequently concentrated at the periphery. Nevertheless, the nucleus is light-staining and has the appearance of being malignant (fig. 12). The cytoplasm is moderate in amount and polyhedral in shape, and frequently exhibits sharp, "pig-tail" corners.

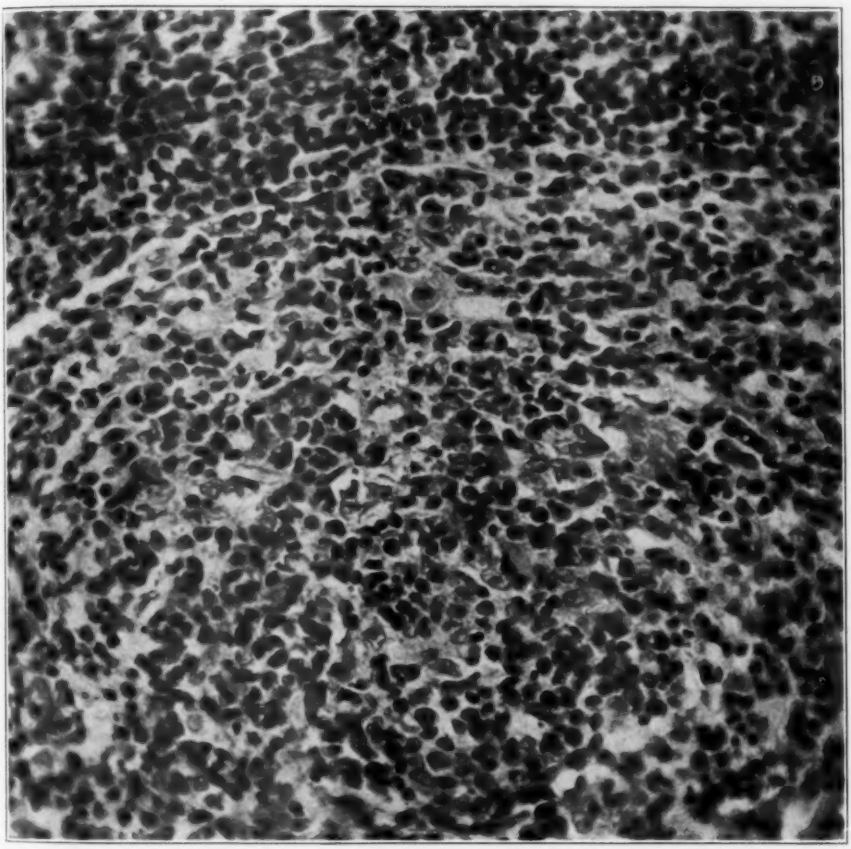

Fig. 9.—Low power photomicrograph of a lymph gland removed at operation for carcinoma of the stomach (Path. no. 41307). It was enlarged and hard and was thought to be involved by metastatic growth. Microscopic examination, however, showed a hyperplastic lymphadenitis, involving the germinal centers. There was no evidence of a malignant process in the section. Note the similarity of these cells to those in figure 10. The cells are large and polygonal, and are not closely packed. They are supported loosely by a moderate amount of reticulum. Larger endothelioid cells may also be seen. The germinal center is surrounded by normal lymphocytes. This is a benign reticuloma.

Reticulum is present but varies in amount with the portion of the tumor. In some areas it is abundant; in others, almost negligible. The cells are not packed closely together and invade the normal structures with every characteristic of malignant growth.

A peculiarity of some of these tumors is the presence of large giant cells (fig. 11). These may be of two types. One contains two or more nuclei, similar to those of the single tumor cells, and gives the impres-

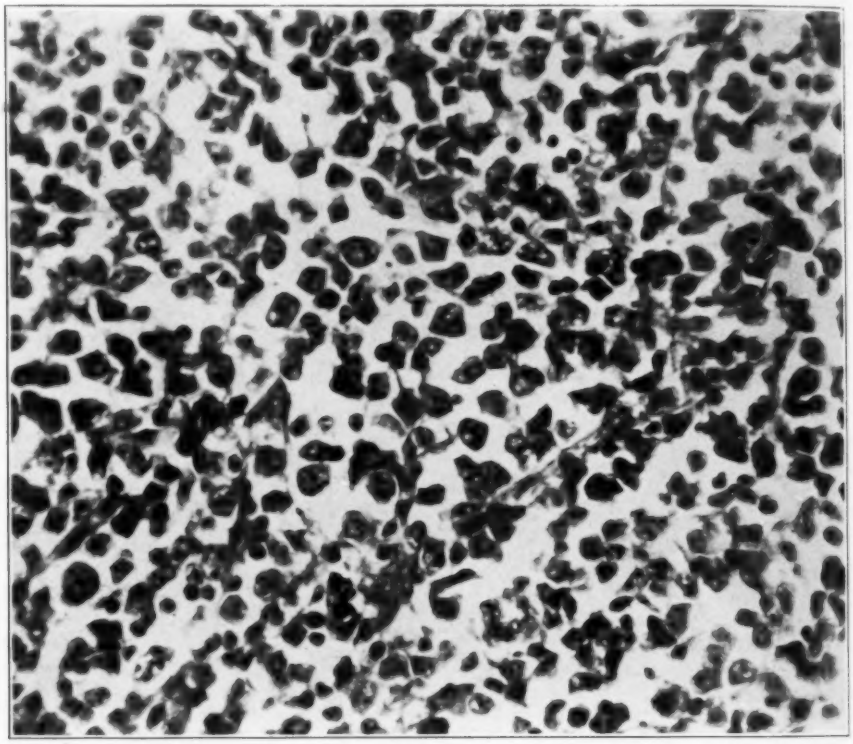

Fig. 10.—Medium power photomicrograph of a malignant reticuloma of the ileum (Path. no. 41291). (From the same case as fig. 2.) Note the large, irregular cells with the "pig-tail" cytoplasm and the reticulum. The cells are not as closely packed as in malignant lymphocytoma.

sion of a cellular fusion. The other is a large cell with a single nucleus, much larger than that of the tumor cell. This nucleus is light-staining and contains less chromatin, but one or two nucleoli. The cytoplasm is darker than the nucleus. Flexner [19] and Libman [6] have called attention to these, suggesting that they may be of parasitic origin and connected with the etiology of the growth.

19. Flexner, S.: Rep. Johns Hopkins Hosp. **3**:153, 1893.

Vascularity is well developed in this type of tumor. Numerous capillaries can be seen, most of which have been invaded by the tumor cells.

An infiltration of small round cells is usually found. This consists of small lymphocytes and plasma cells. Polymorphonuclear leukocytes may be present, especially if secondary infection has taken place. An

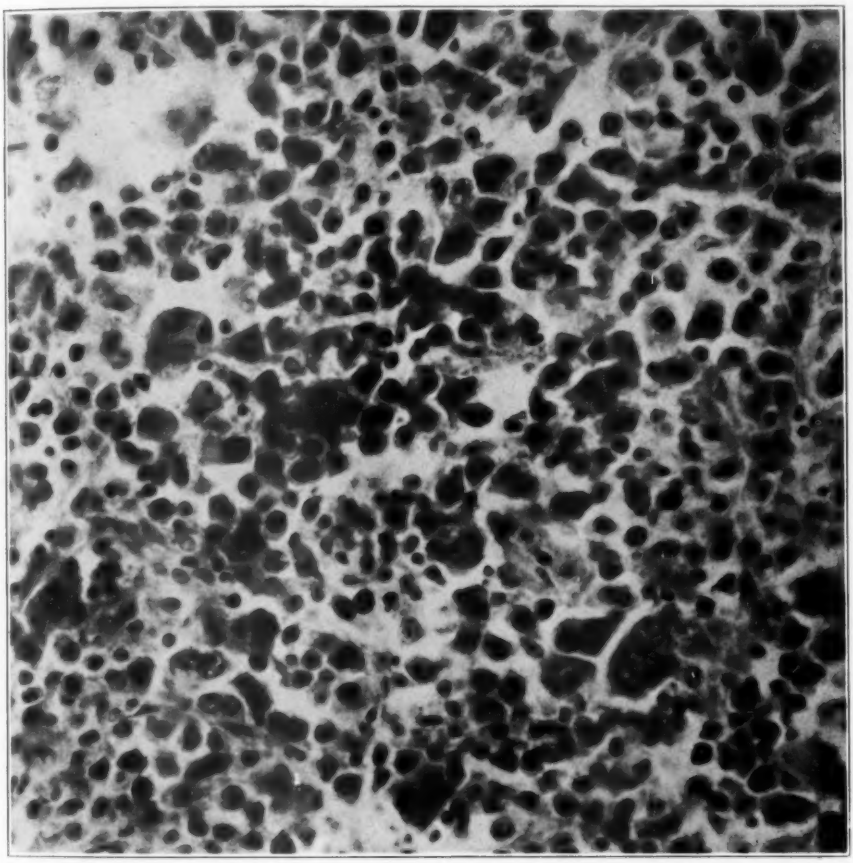

Fig. 11.—Low power photomicrograph of a malignant reticuloma of the colon (Path. no. 32293). This area shows, in addition to the irregular malignant cells pointed out in the preceding photograph, large giant cells which contain two or more nuclei and resemble very much the tumor giant cells found in sarcoma. Eosinophils are present, but cannot be distinguished without their characteristic red granules.

apparent characteristic of the tumor is the presence of numerous eosinophils. This is, of course, more marked in some tumors than in others, but is a fairly constant finding.

PATHOGENESIS

The etiology of the lymphoblastomas is as obscure as that of any tumor. The origin from the lymphoid tissue in the gastro-intestinal tract, however, can hardly be doubted in view of the following confirming factors:

1. The tumors are most frequent in the portions of the tract richest in lymphoid tissue, namely, the lower part of the ileum and cecum.

2. In certain instances the tumor has been observed in an early stage developing in preexisting lymphoid tissue (fig. 13).

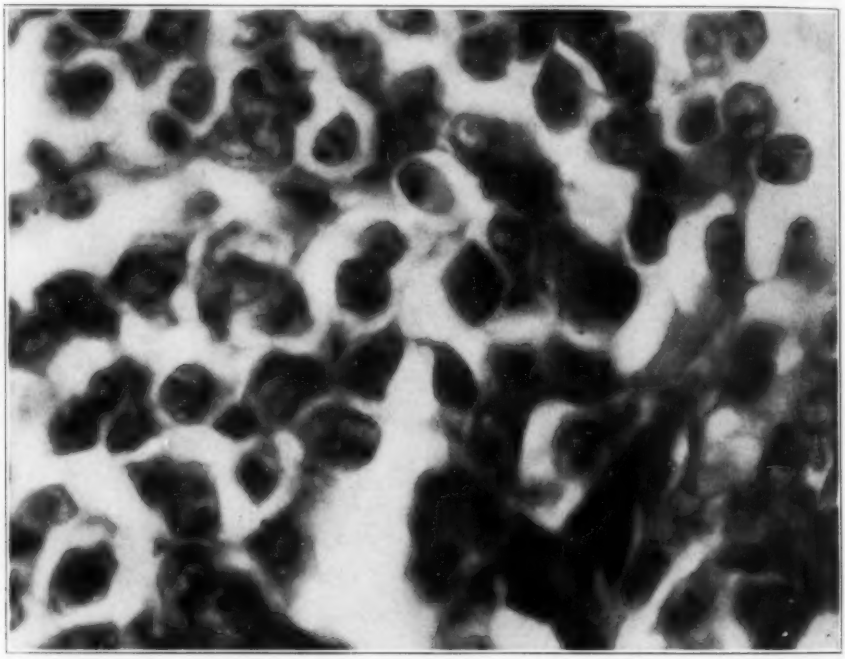

Fig. 12.—High power photomicrograph of a malignant reticuloma of the ileum (Path. no. 41291). (See figs. 2 and 10.) Note the characteristic shape of the cell, the presence of a large amount of reticulum and the character of the nuclei.

3. In tumors, especially of the lymphocytoma group, the development of the tumor cells can be traced from immature lymphocytes.

Assuming this to be true, one is still at a loss to explain the stimulus responsible for tumor formation. Some pathologists regard the tumors as a part of a generalized process such as leukemia, Hodgkin's disease or a nonspecific infection. Undoubtedly this is true in selected cases, but the absence of clinical similarity in the majority precludes the probability. These processes cannot be other than true tumor formations.

While an intricate classification is ambiguous and superfluous, the lymphoblastomas should be further classified to give a satisfactory working knowledge. Ewing classified the tumors arising from lymphoid tissue as follows:

Origin	Anatomic Type	Clinical Type
Lymphocytes:	Lymphocytoma	Simple lymphoma. Tuberculous lymphoma. Lymphatic leukemia. Pseudoleukemia
Reticulum Cells:	Large round cell hyperplasia or neoplasia	Granuloma malignum. Myeloid leukemia. Hodgkin's sarcoma
Endothelial Cells:	Endothelial hyperplasia or neoplasia	Large cell sarcoma. Endothelial hyperplasia of tuberculosis, etc. Endothelioma

The tumors of lymphocytic origin that have been dealt with are therefore lymphocytomas and may be roughly classified benign and malignant. Those of reticulum cell origin may be similarly classed as reticulomas and are likewise benign and malignant.

Benign Lymphocytoma.—Tumors of this group comprise those commonly known as chronic inflammatory tumors, benign granulomas and the intestinal manifestations of certain specific infections such as tuberculosis and syphilis. The tumor cells usually represent a cellular reaction to stimulation of an inflammatory nature.

Malignant Lymphocytoma.—This is the tumor commonly diagnosed small round cell sarcoma. It is a true neoplasm of the lymphocytic cells and possesses all the characteristics of a malignant process, pursuing a progressive course and terminating fatally in the absence of successful intervention. Metastases may occur, but owing to the similarity of the cells to normal lymphocytes, they are frequently overlooked.

Benign Reticuloma.—This is not a true neoplasm but should be included as representative of the benign reticulum cell hyperplasia. Enlarged mesenteric glands are not infrequently found in many conditions. They are especially common in the presence of carcinoma of the bowel, and for this reason are frequently diagnosed as metastases until proved otherwise by histologic examination. It is then found that there is a hyperplasia of the reticulum cells of the lymph node bearing a striking resemblance to certain types of sarcoma.

Malignant Reticuloma.—This type of the reticulum cell sarcoma is apparently a malignant neoplasia of the reticulum cells of the follicles and sinuses. The cells undergo malignant metamorphosis, grow rapidly and metastasize early. No satisfactory explanation has been offered for the presence of the giant cells alluded to in a foregoing paragraph. The parasitic theory of Flexner and Libman is unique, but evidence in support of such a theory is lacking. The eosinophilia is likewise difficult to understand and is a characteristic for which there is no apparent explanation.

MALIGNANCY

The malignancy of the lymphoblastomas is still a debated question. The problem presumably arises from the difficulty experienced by the pathologist in differentiating the benign from the malignant by the use of the microscope. Undoubtedly there are tumors which are benign, and it may be said in defense of the pathologist that from the microscopic picture alone it is difficult to establish the grade of malignancy. Clinical data and the progress of the disease are no more helpful. It should not, however, in view of the characteristics previously mentioned, be difficult to distinguish the lymphocytoma from the reticuloma group.

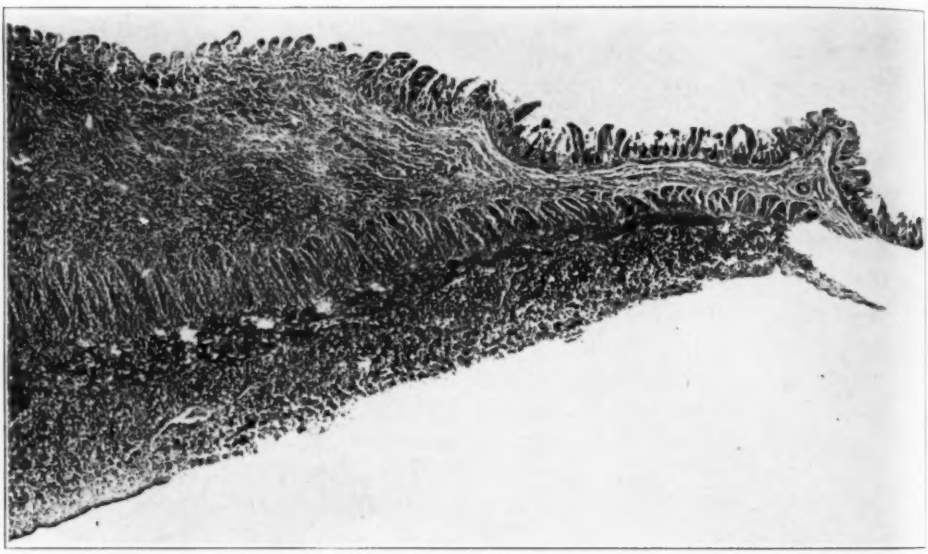

Fig. 13.—Low power photomicrograph of a malignant lymphocytoma developing in a Peyer's patch in the lower part of the ileum (Path. no. 7403). Under high power one can see the remains of normal lymphoid tissue. This tumor was growing in a flat plaque, producing a flattened, oval elevation in the wall of the intestine.

Lymphoblastomas are commonly thought to have a poorer prognosis than carcinomas. This is not wholly true, but varies with the type of tumor. The reticulomas are without doubt more malignant than the lymphocytomas and represent a grade of malignancy comparable to grade IV adenocarcinomas. The lymphocytomas, on the other hand, metastasize late, if at all, and correspond to adenocarcinomas of grades I and II in their manifestations of malignancy.

The fact remains that microscopic differentiation of the benign from the malignant is difficult and frequently impossible. In the light of

present knowledge, however, they must all be regarded as potentially malignant.

PROGNOSIS

Since the lymphoblastomas rarely produce constriction in the early stages of the disease, the condition is not recognized until in its advanced stages. This is partially responsible for the grave prognosis usually associated with the tumor. If recognized early the ultimate mortality would no doubt be less than that of carcinoma. As it is, most of the tumors are diagnosed after they have attained a size sufficient to impair the successful extirpation, and the chances for ultimate recovery are correspondingly poor. In certain cases a superimposed condition such as intussusception may identify the tumor early and thereby enhance the recovery of the patient. One may say in summary, therefore, that, like carcinomas, the prognosis is good when the condition is recognized early and resection is performed. In addition, the factor of earlier metastasis in reticulomas, gives to these a graver prognosis, while lymphocytomas are more apt to be recognized before the condition is inoperable, and respond favorably to operative intervention.

TREATMENT

Surgical intervention offers the best chance of cure if the disease is recognized early. It is preferable to remove the section of intestine containing the tumor regardless of the size of the growth. The mortality attending resection is sufficiently low in competent hands to justify the operation, and although a tumor may appear perfectly benign in the gross, it is best to remove a good margin of healthy tissue. In the larger organs, such as the stomach and cecum, an excision is sometimes necessitated by the location. If this is the case, every effort should be made to remove as wide a margin of healthy tissue as possible. It is also well to remove adjacent glands with the tumor. It is extremely difficult to detect early glandular metastases even in histologic section, but, as has been pointed out, glandular enlargement is common. This in many cases is due to a simple lymphadenitis, but it is wiser to remove the metastases as extensively as possible with the tumor.

Irradiation has been used in a few inoperable cases with satisfactory results. Balfour and McCann [20] have emphasized the favorable result of radium and roentgen therapy, both as a preoperative measure and as a palliative treatment in inoperable cases. The tumors are radiosensitive to a certain degree, and although it cannot be hoped to bring about a complete cure, a temporary cessation of symptoms accompanied by a decrease in the size of the tumor may be expected.

20. Balfour, D. C., and McCann, J. C.: Am. J. Cancer **15**:440, 1931.

TABLE 2.—*Lymphoblastomas of the Gastro-Intestinal Tract (45 Cases)*

Path. No.	Race	Sex	Age	Location	Duration	Chief Symptoms	Treatment	Gross Appearance	Microscopic Type	Result
							Stomach			
44757	W	M	54	Stomach	8 mos.	Progressive weakness and loss of 30 pounds (13.6 Kg.)	Partial resection of stomach; anterior gastro-enterostomy	Thick nodular mass occupying greater curvature of stomach	Benign lymphocytoma	Dead, peritonitis
44477	W	F	54	Stomach	3 yrs.	Weakness; general glandular enlargement; loss of weight	No operation; autopsy specimen	Ulcerated mass in stomach with metastases to liver and regional glands	Malignant reticuloma	Dead, pneumonia
43525	W	M	50	Stomach	.....	Palpable epigastric mass, subjectively increasing in size	Exploratory laparotomy for inoperable carcinoma of stomach; biopsy	Large lymph gland	Malignant reticuloma	Dead, metastases
37370	W	F	29	Stomach	3 wks.	Slight gastric upset with eructation and distention	Partial resection of stomach	Thick, ulcerated mass in wall of stomach	Malignant lymphocytoma	Lost
32582	W	M	62	Stomach	6 mos.	Belching, indigestion and loss of weight	Partial resection of stomach	Ulcerated mass in wall of stomach	Malignant lymphocytoma	Dead, postoperative embolus
28681	W	M	52	Stomach	18 mos.	Pain, belching, vomiting and distention	Partial resection of stomach	Large, thick ulcer	Malignant lymphocytoma	Dead, 1 year, recurrence
25018	C	M	55	Stomach	6 wks.	Vomiting; diarrhea	Partial resection with posterior gastro-enterostomy	Large, fungating ulcer, perforating	Malignant lymphocytoma	Dead, postoperative shock
15400	W	M	57	Stomach	3 yrs.	Indigestion; epigastric distress	Partial resection with posterior gastro-enterostomy	Nodular mass, the size of a dollar, in wall of stomach	Malignant lymphocytoma	Lost
G 10900	W	M	51	Stomach	3 yrs.	Indigestion; loss of weight	Exploratory laparotomy for inoperable carcinoma of stomach; autopsy specimen	Wall of stomach indurated diffusely; metastases to liver and lungs	Malignant reticuloma	Dead, metastases
G 10816	W	M	55	Stomach	9 mos.	Loss of weight; weakness; melena	Partial resection of stomach with anterior gastro-enterostomy and entero-enterostomy	Large ulcerated mass on lesser curvature; metastases to regional nodes	Malignant reticuloma	Dead, metastases
G 9074	W	M	66	Stomach	9 mos.	Anorexia; dyspnea; swelling in abdomen	No operation; autopsy specimen	Huge tumor, soft, ragged and ulcerated	Malignant reticuloma	Dead
G 7403	W	M	56	Stomach	1 yr.	Gnawing pain; eructation; vomiting; loss of weight	No operation; autopsy specimen	Hard, irregular mass, freely movable, ulcerated, involving pancreas, gallbladder, cecum and rectum	Malignant lymphocytoma	Dead, metastases
4509	W	F	..	Stomach	.....	.....	Pylorectomy	.....	Malignant lymphocytoma	Lost

						Small Intestine				
44950	W	F	50	Ileum	1 yr.	Weakness; loss of 30 pounds (13.6 Kg.); palpable mass	Resection of terminal part of ileum; entero-colostomy	Hard, annular tumor	Malignant reticuloma	Well *
44221	C	F	46	Ileum	6 mos.	Malaise; cramplike pain; diarrhea; nausea	Resection of terminal part of ileum; entero-colostomy	Annular, sacculated tumor	Malignant reticuloma	Living, 3 years, recurrence
41291	W	M	47	Ileum	.....	Burning and soreness in epigastrium; "bloating"	Resection of portion of ileum; lateral entero-enterostomy	Large, sacculated tumor surrounding lumen	Malignant reticuloma	Dead, recurrence
39264	W	F	36	Ileum	6 mos.	Diffuse, dragging pain in lower part of abdomen	Resection; end-to-end anastomosis	Annular tumor in distal portion	Malignant reticuloma	Unknown
38092	W	M	33	Ileum	2 mos.	Intermittent, diffuse pain in lower part of abdomen	.....	.....	Malignant lymphocytoma	Unknown
34318(2)	W	F	19	Ileum	5 yrs.	Anemia, eructation and constipation	Excision of small nodule from duodenum	Small, papillary nodule in wall of ileum	Malignant reticuloma	Improved
36806	W	F	9	Ileum	2 wks.	Pain in right side	Resection of terminal part of ileum and cecum	An ileocecal, annular tumor producing intussusception	Malignant lymphocytoma	Well
27187	C	M	18	Ileum	24 hrs.	Acute pain; vomiting; weakness	Resection	Gangrenous, intussusception produced by multiple, sessile tumor	Malignant lymphocytoma	Dead, peritonitis
26163	W	M	5	Ileum	.....	.....	Resection of part of ileum with anastomosis	Firm, annular, spherical tumor	Malignant lymphocytoma	Well
24971	W	M	6 mos.	Ileum	4 wks.	Diffuse, cramplike pains; vomiting; melena	Partial resection of ileum	Annular tumor producing gangrenous intussusception	Malignant reticuloma	Dead, recurrence
18427	W	M	39	Ileum	7 wks.	Constipation; nausea; vomiting; cramps; blood-streaked stools; loss of weight	Resection of cecum and ileum	Hard, annular tumor producing intussusception	Malignant lymphocytoma	Well
16485a	C	M	24	Ileum	.....	Acute intestinal obstruction	Resection of part of ileum	Multiple polypoid tumor causing intussusception	Malignant lymphocytoma	Well
G 10140	W	M	77	Ileum	6 mos.	Difficulty in urination	No operation; autopsy specimen	Tumor external to lumen, ulcerated	Malignant lymphocytoma	Dead, uremia
G 7492	W	M	12	Ileum	.....	Stricture of larynx	No operation; autopsy specimen	Nodular elevation surrounding a polypoid growth	Malignant lymphocytoma	Dead, asphyxia
G 6346	W	M	37	Ileum	1 mo.	Nausea; vomiting; headaches; loss of vision; mental deterioration	Craniotomy for brain tumor; dead; post-operative autopsy specimen	Multiple, small sessile tumors, hard and ulcerated; metastases to brain	Malignant reticuloma	Dead, metastases
G 4729	W	F	42	Duodenum	6 wks.	Pneumonia; anemia; swelling	No operation; autopsy specimen	Stony hard, nodular elevation	Malignant lymphocytoma	Dead, pneumonia
G 2496	W	M	57	Ileum	1 yr.	Malaise; severe prostration after influenza	No operation; autopsy specimen	Thickening; ulcerated plaque in ileum	Malignant lymphocytoma	Dead, pneumonia
G 1842	W	M	17	Ileum	3 mos.	Constipation; pain	No operation; autopsy specimen	Large, hard, nodular tumor, ulceration	Malignant lymphocytoma	Dead
G 225	W	M	27	Ileum	4 mos.	Diarrhea; vomiting; painful urination	No operation; autopsy specimen	Three tumors, causing partial obstruction	Malignant lymphocytoma	Dead
UM	W	M	69	Ileum	3 wks.	Malaise; indigestion; irregular pulse	Incision and drainage; large abscess attached to ileum	Necrotic mass size of a grapefruit	Malignant reticuloma	Dead, peritonitis

* The term "well" signifies that the patient lived five years or longer after operation.

TABLE 2.—*Lymphoblastomas of the Gastro-Intestinal Tract (45 Cases)—Continued*

Path. No.	Race	Sex	Age	Location	Duration	Chief Symptoms	Treatment	Gross Appearance	Microscopic Type	Result
							Colon			
41660	W	F	50	Cecum	10 days	Pain and constipation in right lower quadrant	Resection of ileum and cecum; lateral ileocolostomy	Sessile tumor in cecum	Malignant lymphocytoma	Dead, recurrence
32293	C	M	42	Cecum	2 mos.	Pain; bleeding; constipation	Resection of ileum and cecum; lateral anastomosis; ileocolostomy	Pedunculated mass at ileocecal valve; obstruction	Malignant reticuloma	Lost
29605	W	F	9	Cecum	3 wks.	Bleeding; pain; vomiting; mass in right lower quadrant	Resection of ileum and cecum; lateral anastomosis; ileocolostomy	Tumor of cecum extending over into ileum	Malignant lymphocytoma	Lost
29688	W	M	41	Sigmoid	1 yr.	Constipation; dull pain in left lower quadrant; bleeding	Exploratory laparotomy for inoperable carcinoma of sigmoid	Autopsy: large tumor, nodular, size of fist, filling pelvis	Malignant reticuloma	Dead, metastases
28312	W	F	45	Cecum	10 days	Pain and tenderness in left lower quadrant	Resection of cecum and ileum; later anastomosis; ileocolostomy	Thickened, indurated wall of cecum	Malignant lymphocytoma	Dead, extension
22763	W	M	41	Cecum	6 wks.	Dull, burning pain; tenderness	Resection of cecum and transverse colon; lateral ileocolostomy	Two small nodules, 2 cm. in diameter in cecum	Malignant reticuloma	Lost
22475	W	M	10	Cecum	1 yr.	Pain and colic	Resection of cecum and ileum; lateral anastomosis; ileocolostomy	.....	Malignant reticuloma	Lost
13564	W	F	68	Cecum	7 mos.	Nausea; vomiting; palpable mass	Resection of cecum and ileum; lateral anastomosis; ileocolostomy	Large, hollow growth of cecum; ileum adherent	Malignant reticuloma	Dead, pneumonia
12722	W	M	56	Cecum	5 mos.	Pain, right lower quadrant; lump felt 3 weeks	Resection of cecum and lateral ileocolostomy	Large tumor of cecum	Malignant lymphocytoma	Well
8230	W	M	33	Cecum	3 yrs.	Diffuse gastro-intestinal upsets; pain; nausea; vomiting	Resection of cecum and portion of ileum; ileocolostomy	Large tumor of cecum; thickened, indurated walls	Malignant reticuloma	Dead, 3 months, recurrence
9055	W	F	3	Cecum	4 mos.	Colic and vomiting, intermittently	Resection of cecum and portion of ileum; lateral ileocolostomy	Cecum partly invaginated and filled by firm growth	Malignant reticuloma	Dead, 1 month, recurrence
							Rectum			
12284	W	F	75	Rectum	6 mos.	Pain in rectum and constipation	Local excision of portion of rectum with cautery	Irregular strands and large masses of tumor tissue	Malignant reticuloma	Dead, 1 year, recurrence

CONCLUSIONS

1. Forty-five cases of lymphoblastomas, formerly diagnosed as sarcomas, chronic inflammatory tumors, lymphomas or other types of growth, have been reviewed from the standpoint of their clinical and pathologic features.

2. These tumors frequently occur in young children. The site of election is the terminal part of the ileum and cecum.

3. It is difficult clinically to distinguish lymphoblastomas from carcinomas, but certain characteristics of the former have been emphasized, such as an insidious onset without acute pain, severe wasting and secondary anemia. The presence of a moderate degree of fever and the absence of early symptoms of obstruction are strongly suggestive of a tumor of lymphoid origin.

4. The characteristic gross form produced is an aneurysmal dilatation of the bowel in contradistinction to the stenosis produced by carcinoma. The typical cytologic form is that of a round cell, resembling those of the lymphoid series. The tumors are divided into two main groups, the lymphocytomas and the reticulomas, according to the cells from which they arise.

5. These tumors are thought to arise from the lymphoid tissue of the intestinal tract and represent atypical developments of the lymphocytic and reticulum cells.

6. The majority of the tumors are malignant. The remainder must be considered potentially malignant, although it is frequently impossible to distinguish the malignant characteristics. Tumors of the reticulum cell type are the more malignant. Both are frequently confused with benign inflammatory lesions such as tuberculosis and syphilis.

The prognosis is poor, owing to the late diagnosis. Optimum treatment consists of surgical resection combined with irradiation.

EROSION OF FEMORAL ARTERY, SECONDARY TO PATHOLOGIC FRACTURE DUE TO OSTEOMYELITIS

REPORT OF A CASE IN WHICH THE COMMON FEMORAL ARTERY WAS LIGATED

JACOB KULOWSKI, M.D.
AND
MANUEL E. PUSITZ, M.D.
IOWA CITY

The chief interest in reporting this case is the ligation of the common femoral artery because of secondary hemorrhage incident to the erosion of the vessel. The second feature is the presence of two pathologic fractures, one of the surgical neck of the humerus, and the other in the shaft of the femur, the latter being directly responsible for the erosion of the superficial femoral artery.

Pathologic fracture in osteomyelitis can be prevented in practically all cases treated by the Orr method primarily. Over two hundred patients have been treated by the Orr method in this clinic since 1923, with only one case of secondary pathologic fracture. This occurred in a femur which went unprotected by the usual plaster hip spica for only one day. This same patient, who had multiple lesions, completely recovered.

The possibility of secondary hemorrhage, especially of mechanical trauma incident to pathologic fracture, makes Orr's dictum of adequate rest and protection following the primary adequate drainage absolutely essential in the treatment of osteomyelitis. This principle, in our opinion, cannot be ignored, regardless of the method used in the treatment of pyogenic involvement of bone.

Ligation of the common femoral artery is not a frequent procedure, except as a life-saving measure, preliminary to amputation. The collateral circulation of this part of the femoral vessel is certainly more efficient than is usually considered to be the case. In this patient amputation was performed no less than twenty-eight days after the ligation. This was necessary because of the septic absorption from the extensively involved femur.

From the Department of Orthopedic Surgery, State University of Iowa, Service of Dr. Arthur Steindler.

REPORT OF A CASE

In Avis C., aged 13, white, the onset of the present illness was typically acute, following a moderate trauma to the right knee. After a stormy period of seven weeks, the right thigh was finally but inadequately drained by two soft tissue stab wounds. One week before her admission to the hospital she moved her right leg, and experienced severe pain and a sense of breaking in the right thigh.

Fig. 1.—*A*, the patient on her admission to the hospital, Jan. 20, 1932; *B* and *C*, the lateral and anteroposterior roentgenograms of the right femur. The lower two thirds of the shaft is involved. There is remarkably little displacement at the pathologic fracture site.

On admission to the hospital on Jan. 20, 1932, she was in great pain, and was markedly emaciated. On examination, the right thigh was enlarged, tender, bowed anterolaterally, and crepitated on gentle manipulation. The right shoulder was tender and fluctuating, and grated.

The temperature ranged from 101 to 104 F., the pulse from 110 to 150, and the respirations around 40. The leukocyte count was 13,400, the hemoglobin 80 per cent and the red cell count 3,620,000. The urine was normal, and the Wassermann tests negative, but the intradermal tuberculin tests, both human and bovine, were positive on several occasions. The blood cultures were negative. The coagulation period was three minutes.

The child was extremely septic on admission, the period of her illness now being of thirteen weeks' duration. The active pulmonary findings were suggestive of tuberculosis. All these factors made the operative risk too great. A hip spica

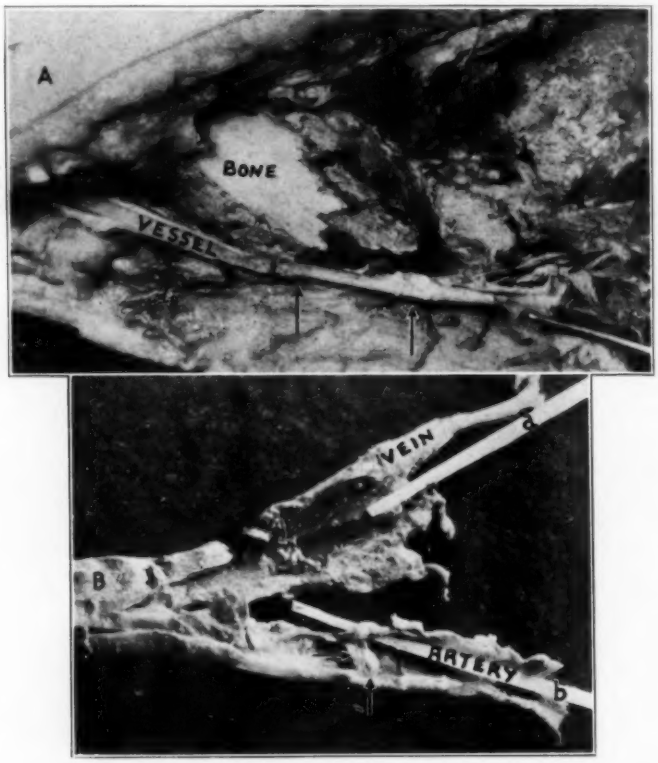

Fig. 2.—*A*, postamputation dissection of the right thigh and femur. The arrows indicate the contact points of the vessels with the jagged distal fragment. *B*, the superficial femoral artery and vein dissected free and opened. The venous defect (*a*) could not definitely be attributed to erosion. The artery with the indicator passing through the erosion is shown by *b*. In the lumen, contiguous to the opening but not entirely blocking it, is observed an organized thrombus.

was applied under anesthesia, and further hygienic measures instituted to improve the patient's resistance.

On February 10, Orr drainage was done on the right femur through a window in the cast. Free pus was not encountered except in Scarpa's triangle. The bone in the region of the fracture was necrotic, exhibiting a somewhat yellowish, caseous appearance, suggesting tuberculosis. Guinea-pig inoculation and microscopic

examination of tissue gave negative results. The bacteriologic examination proved Staphylococcus albus to be the etiologic agent. The recovery was uneventful.

On March 16, the sequestrated upper half of the right humerus was gently removed from a sinus located over the upper lateral aspect of the shoulder, without anesthesia.

The first massive hemorrhage suddenly occurred about one month after the operation on the femur. The patient rapidly exhibited symptoms of shock and finally syncope. Examination of the wound failed to reveal any actively bleeding

Fig. 3.—The amputated right lower extremity twenty-eight days after ligation of the common femoral artery. Except for the discoloration of the heel, the parts are in excellent condition. The terminal vessels are impermeable to the opaque solution injected immediately after amputation.

points. Transfusion of citrated blood and dextrose administered intravenously revived her. In the next two days she had two more extensive hemorrhages, from which she recovered following the same treatment.

Immediately after the third hemorrhage, the right common femoral artery was ligated directly below Poupart's ligament, under local anesthesia in the ward.

On regaining consciousness, the patient complained of numbness of the entire extremity, and pain over the dorsum of the foot and heel. The foot remained cold and colorless for the remainder of that day. On the second day the foot became

warm, but was still somewhat painful. The extremity, below the knee, exhibited almost complete anesthesia during the entire period of observation until amputation. There was no level of hyperesthesia noted at any time. Of particular interest was the observation that no ischemic contractures occurred. Following ligation, the red cell count steadily rose from less than 2,000,000 to about 4,000,000 at the time of discharge from the hospital. No further hemorrhages ensued.

Septic absorption necessitated further drastic measures, and twenty-eight days after ligation, a Guillotine amputation of the right thigh was done at the junction

Fig. 4.—The patient two months after amputation, and the roentgenogram of the stump of the same period.

of the upper and middle thirds of the thigh, which was just above the site of the pathologic fracture.

The amputated extremity was immediately dissected, and the superficial femoral artery was found to be eroded opposite the jagged distal fragment, at which point the vessel was in contact with the bone. The accompanying vein also presented a defect which could not be absolutely ascertained as being due to erosion. On opening the femoral artery, an organized thrombus was found contiguous to the erosion, but not completely blocking it. The muscles of the leg were pale, but otherwise not remarkable. Histologic examination of the vessel wall, thrombus and a section of the gastrocnemius muscle revealed: erosion of the femoral artery, organizing

thrombus and ischemia of the muscle. The superficial femoral artery was then injected at its uppermost limit with an opaque solution, and roentgen examination was made. All the vessels filled readily except the terminal phalangeal branches. Further dissection corroborated these roentgen findings.

The patient made an uneventful recovery, and was discharged about two months after the last operative procedure. The stump was almost completely healed.

COMMENT

Several questions readily present themselves regarding the treatment in such a case. It may be stated at the outset that this extreme degree of involvement will not likely occur if adequate primary drainage is established as soon as the diagnosis of osteomyelitis is made.

1. Should primary amputation be considered at the first examination of a patient presenting this picture?

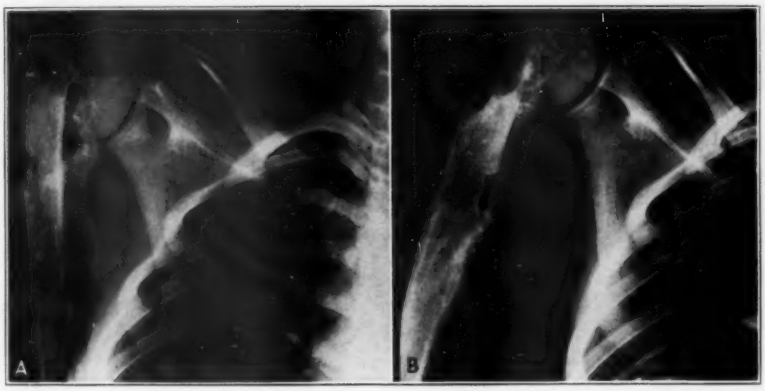

Fig. 5.—*A*, roentgenogram of the right shoulder on the patient's admission, showing the pathologic fracture of the surgical neck of the humerus. The upper one half of the shaft is sequestrated. *B*, the same shoulder three months after sequestrectomy. The head of the humerus is apparently viable and is united to the distal fragment. The functional result is good.

Many limbs have been spared in this clinic by following the regimen as instituted in the case reported. A primary adequate cast, in the great majority of cases, will enable the patient to develop sufficient resistance to combat the infection, after final drainage has been established. Amputation is resorted to only as a life-saving measure. Cases are on record in this clinic that wholly substantiate this procedure.

2. What is the danger of secondary hemorrhage following an extensive drainage of the femur?

It is minimum if the operator confines himself to the lateral side of the thigh, and limits his manipulations to blunt dissection in the region of the great vessels.

3. Can one cope successfully with a secondary hemorrhage when a cast has been applied?

The window in the cast can readily be removed if necessary, and the operative field quickly exposed. The cast will certainly minimize the patient's early excitable movements and tend to lessen the degree of hemorrhage.

4. Is it safe to operate through a window in the cast, as advocated by Orr?

The window should be adequate to permit easy access to all parts of the field of operation. This method saves so much time in poor risks, that the possible disadvantages are outweighed by the benefits to the patient.

CONCLUSION

A case has been reported of ligation of the common femoral artery secondary to erosion of the vessel incident to a pathologic fracture in osteomyelitis. To the list of complications of osteomyelitis is added and elaborated erosion of the femoral artery, which has been but seldom reported in the literature. Special emphasis has been placed on the prevention of pathologic fracture in osteomyelitis by adequate protection as advocated by Orr.

BLOOD SUPPLY OF THE LARGE INTESTINE

ITS SURGICAL CONSIDERATIONS

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HISTORICAL

The historical background for the blood supply of the colon does not extend beyond Galen[1] (131-201 A.D.), as he was the first to describe arteries as carriers of blood. However great Galen's services may have been to medicine in his day, his influence in the long run was retrogressive. Philosophy was an integral part of the learning of every scholar of his time, and philosophic beliefs and concepts were inextricably mingled with scientific facts. Galen might have discovered many more anatomic and physiologic facts had he not hidden science behind a screen of theory regarding the spirits of the body. Bodily functions were ascribed to the agency of these spirits, and research was abandoned when the spirits entered. One result of this philosophic belief is evidenced in Galen's anatomic diagrams,[2] which show vessels coursing vaguely from intestine to liver, but nothing definite and clearcut.

In the following centuries and in the Middle Ages, Christianity replaced philosophy as a stumbling block to advance in the knowledge of anatomy.[3] Owing to ascetic doctrine, the body was regarded as the temporary and unworthy abode of the soul during life, and in illness treatment of the soul was almost always incorporated with, if not substituted for, measures to relieve the body. However, with death came a change in attitude toward the body, which was looked on now as a sacred relic with which the soul would some day reunite. These two

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From the Division of Surgery, the Mayo Clinic.

1. Buck, A. H.: The Growth of Medicine, New Haven, Conn., Yale University Press, 1917, p. 169; Cyclopaedia of Anatomy and Physiology, London, Longman, Brown, Green, Longmans & Roberts, 1835-1836, vol. 1, p. 220. Garrison, F. H.: An Introduction to the History of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1929.

2. Singer, C. J.: The fasciculo di medicina, Florence, R. Lier & Co., 1925, plate 63.

3. Singer, C J.: The Evolution of Anatomy, New York, Alfred A. Knopf, 1925.

strangely antipathetic ideas were powerful factors in keeping exact knowledge of what was within the body at a minimum and in preventing discovery of the details of anatomy. An illustration in a late thirteenth century provincial manuscript [4] shows loops of intestine with indefinite vessels. The arterial diagrams of Vesalius [5] about 1538 indicate the inferior mesenteric artery but confuse the superior mesenteric artery and the celiac axis. More than a century later (1653), Culpepper [6] shows the same confusion in his translation of Veslingius' work. It is paradoxical that the anastomosis of the mesenteric arteries should be named for Jean Riolan, as Riolan,[7] to whom Harvey [8] refers as "prince of anatomists," is famous for his opposition to Harvey's principle of the circulation of the blood.

After the acceptance of the idea of the circulation of the blood, von Haller,[9] writing between 1759 and 1766, gave a thorough and comprehensive description of the blood supply of the colon. The emphasis he placed on the blood supplied by anastomosis from the hypogastric, spermatic, intercostal, capsular and lumbar arteries probably started some of the misconceptions regarding them. However, von Haller established the fact that the primary blood supply of the colon is from branches of the superior and inferior mesenteric arteries, and that the adjacent branches anastomose near the wall of the colon. With the exception of variations of individual branches (which will be considered separately) and detail of description, the following anatomists agree with the fundamental outline of von Haller: Cheselden,[10] Cruveilhier,[11] von Behr,[12] Wilson,[13] Smith,[14] Henle,[15] Hyrtl,[16] Quain,[17] Treves,[18]

4. Chouland, J. L.: History and Bibliography of Anatomic Illustrations, Chicago, University of Chicago Press, 1920, p. 55.

5. Vesalius, Andreas: Des Andreas Vesalius sechs anatomische Tafeln vom Jahre 1538, in Lichtdruck neu herausgegeben und der 86 Versammlung Deutscher Naturforscher und Arzte zur Feier der 400 Wiederkehr des Jahres seiner Geburt dargeboten von Moriz Holl und Karl Sudhoff, Leipzig, J. A. Barth, 1920.

6. Veslingius, Joannes: The Anatomy of the Body of Man, translated by Nicholas Culpepper, London, P. Cole, 1653.

7. Riolan, Jean, quoted by Eycleshymer, A. C.: Anatomical Names, New York, William Wood & Company, 1917, p. 321.

8. Harvey, William: De motu cordis, London, Nonesuch Press, 1928, p. 121.

9. von Haller, Albert: First Lines of Physiology, Troy, Obadiah Penniman & Co., 1803, p. 368.

10. Cheselden, William: The Anatomy of the Human Body, ed. 13, London, 1792, p. 188.

11. Cruveilhier, Jean: Anatomy of the Human Body, New York, Harper & Bros., 1844, p. 509.

12. von Behr, Alfred: Handbook of Human Anatomy, Philadelphia, Lindsay & Blakiston, 1847, p. 323.

13. Wilson, Erasmus: A System of Human Anatomy, Philadelphia, Blanchard & Lea, 1858, p. 323.

Sobotta,[19] Sappey,[20] Spalteholz,[21] Gray,[22] Cunningham,[23] Morris,[24] Merkel,[25] Toldt,[26] Gerrish,[27] Hartmann,[28] and Piersol.[29] None of the writers disagreed with the conception generally accepted of the blood supply of the colon.

THE COLON

The study of the blood supply of the colon, from the ileocecal valve to the iliac colon or sigmoid, was made with tissue removed at necropsy. More than eighty specimens were removed and examined, but only forty, in which the blood supply of the entire part could be determined exactly, and casts or roentgenograms preserved, are used in this report. Two slightly different methods were followed in this study. The first method consisted of removal, inspection, injection of celluloid solution into the arteries and corrosion of the tissue; the second method consisted of injection of the arteries in situ with a solution of red lead, removal of the specimen, roentgenologic examination and inspection of the specimen. The study of the arteries of the wall of the colon was made by: (1) inspection of the celluloid casts, (2) stereoscopic roentgenograms and flat roentgenograms of the wall of the colon, (3) serial

14. Smith, H. H.: Anatomical Atlas, Philadelphia, Blanchard & Lea, 1859, p. 148.

15. Henle, F. G. J.: Handbuch der systematischen Anatomie des Menschen: Gefässlehre, Braunschweig, F. Vieweg und Sohn, 1871, vol. 3, pt. 1, pp. 161 and 295.

16. Hyrtl, Joseph: Handbuch der topographischen Anatomie, Vienna, W. Braumüller, 1871.

17. Quain, Jones: Elements of Anatomy, London, Longmans, Green & Co., 1914, vol. 2, pt. 2, p. 129.

18. Treves, Frederick: The Anatomy of the Intestinal Canal and Peritoneum in Man, London, H. K. Lewis, 1885.

19. Sobotta, Johannes: Atlas and Text-Book of Human Anatomy, Philadelphia, W. B. Saunders Company, 1907, vol. 3, p. 57.

20. Sappey, quoted by Potherat, Bull. Soc. anat. de Paris **3**:233 (March) 1889.

21. Spalteholz, Werner: Hand-Atlas of Human Anatomy, Philadelphia, J. B. Lippincott Company, 1922, vol. 2, p. 442.

22. Gray, Henry: Anatomy of the Human Body, Philadelphia, Lea & Febiger, 1924, p. 930.

23. Cunningham, D. J.: Text-Book of Anatomy, ed. 5, New York, William Wood & Company, 1921, pp. 41-79; 930-933; 1162; 1220-1222 and 1249-1256.

24. Morris, Henry: Human Anatomy, ed. 7, Philadelphia, P. Blakiston's Son & Co., 1923, pp. 633 and 1204.

25. Merkel, Friedrich: Die Anatomie des Menschen, Wiesbaden, J. F. Bergmann, 1918, vol. 6, p. 143.

26. Toldt, Karl: An Atlas of Human Anatomy, New York, Rebman Co., 1919.

27. Gerrish, F. H.: A Textbook of Anatomy by American Authors, Philadelphia, Lea Bros. & Co., 1899, p. 429.

28. Hartmann, Henri: Some Considerations upon High Amputation of the Rectum, Ann. Surg. **50**:1091 (Dec.) 1909.

29. Piersol, G. A.: Human Anatomy, Philadelphia, J. B. Lippincott Company, 1919, pp. 802 and 1672.

section of the wall of the colon and microscopic examination and (4) dissection of the wall of the colon under lower power magnification.

First Method.—The removal was planned to include all of the arteries supplying the colon from their origins. The small bowel was removed from within 12.5 cm. of the ileocecal valve to the duodenojejunal flexure, the omentum was cut close to the greater curvature of the stomach and reflected downward, the peritoneum was incised lateral to the ascending and descending colon, across the brim of the true pelvis and along the upper border of the pancreas, and the colic ligaments were cut close to their mural attachments. Along the lateral incisions, the colon, the peritoneum, the colic vessels and the subperitoneal fat were reflected toward the median line. At the duodenojejunal flexure the peritoneum was incised close to the bowel and reflected mesially from the anterior surface of the duodenum. The mesocolon was reflected downward from the anterior surface of the pancreas and duodenum. The superior mesenteric artery was severed immediately distal to the origin of the inferior pancreaticoduodenal artery, the entire mass reflected downward, the inferior mesenteric artery cut at its origin and the reflection continued to the pelvic brim where the sigmoid and sigmoid arteries were cut across. The entire mass was removed from the abdominal cavity.

The specimen, consisting of the omentum, the entire colon with its peritoneal attachments and arteries, was subjected to careful examination and the measurements of each specimen were recorded on a printed form. The length and size of the different parts of the colon and the origin and course of the main arteries and marginal artery were recorded.

Thirty-five unembalmed specimens were used for injection of celluloid solution into the arteries and subsequent corrosion of the tissue. The process, with a few modifications, was similar to that used in studies of the blood supply of other organs by Barker,[30] Whitten,[31] Pope and Judd,[32] and Counseller and McIndoe.[33] The lumen of the colon as well as the arteries was injected in eighteen specimens.

The advantage of this method is that an accurate cast of the complete arterial supply of the specimen is preserved and the results of the

30. Barker, N. W.: Celluloid Corrosion Technic for Study of Normal and Pathologic Variations of the Arteries of the Kidney, J. Lab. & Clin. Med. **14**:257 (Dec.) 1928.

31. Whitten, M. B.: A Review of the Technical Methods of Demonstrating the Circulation of the Heart; a Modification of the Celluloid and Corrosion Technic, Arch. Int. Med. **42**:846 (Dec.) 1928.

32. Pope, C. E., and Judd, E. S.: The Arterial Blood Supply of Sigmoid, Rectosigmoid and Rectum, S. Clin. North America **9**:957 (Aug.) 1929.

33. Counseller, V. S., and McIndoe, A. H.: Dilatation of the Bile Ducts (Hydrophepatosis), Surg., Gynec. & Obst. **43**:729 (Dec.) 1926.

inspection are checked. The disadvantage lies in the technical difficulties of removal, injection and subsequent handling of the bulky, fragile specimens.

Second Method.—The arteries of fifteen specimens were injected in situ with opaque material; the specimens were then removed, roentgenograms were taken, specimens were inspected and the results recorded. The inferior mesenteric artery was clamped at its origin from the aorta and the sigmoid arteries, and the marginal artery of the sigmoid was clamped at the brim of the pelvis. The superior mesenteric artery was isolated and severed just distal to the origin of the inferior pancreaticoduodenal artery. A syringe was tied into the distal end of the artery and the vessel was washed with water until the blood disappeared from the fine vessels of the intestine. A warm, hemogenous mixture of about three parts corn starch, two parts red lead and four parts warm water was injected with a syringe. When the small vessels of the intestine were filled, the injection was stopped and the specimen was undisturbed for several hours so that the starch might harden.

The specimen was removed in a manner similar to that described in the first method. It was then spread to its full extent on an aluminum tray with a film immediately beneath, the lumen of the bowel was filled with water, and plates were made for stereoscopic study. The specimen was inspected as in the first method, the results being checked by the roentgenograms. The advantage of this method over the first is that it presents far less technical difficulty.

Embryology.—A brief review of the embryologic development of the colon will give a clearer idea of the condition found in the adult and enables better evaluation of reported anomalies of the blood supply.

Arey,[34] Bailey and Miller,[35] Broman,[36] Dott,[37] Cunningham,[23] Huntington,[38] Jordan,[39] McMurrich,[40] Mall,[41] Morris,[24] Frazer and

34. Arey, L. B.: Developmental Anatomy: A Text-Book and Laboratory Manual of Embryology, Philadelphia, W. B. Saunders Company, 1924.

35. Bailey, F. R.: Textbook of Histology, ed. 7, New York, William Wood and Company, 1927. Bailey, F. R., and Miller, A. M.: Text-book of Embryology, ed. 4, New York, William Wood and Company, 1923.

36. Broman, Ivar: Normale und abnorme Entwicklung der Menschen, Wiesbaden, J. F. Bergmann, 1911.

37. Dott, N. M.: Anomalies of Intestinal Rotation: Their Embryology and Surgical Aspects with Report of Five Cases, Brit. J. Surg. **11**:251 (Oct.) 1923.

38. Huntington, G. S.: The Anatomy of the Human Peritoneum and Abdominal Cavity, Philadelphia, Lea Bros. & Co., 1903.

39. Jordan, H. E.: A Text-Book of Histology, New York, D. Appleton and Company, 1924.

40. McMurrich, J. P.: The Development of the Human Body, ed. 7, Philadelphia, P. Blakiston's Son & Co., 1923, p. 307.

41. Mall, F. P.: Development of the Human Intestine and Its Position in the Adult, Bull. Johns Hopkins Hosp. **9**:197 (Sept.-Oct.) 1898.

Robbins,[42] Pernkopf,[43] Hertzler,[44] Prentiss and Arey,[45] and Piersol[29] are in agreement regarding the principal changes that take place in the embryologic development of the intestinal tract.

In the stage of the primitive streak, an infolding of the entoderm and the splanchnic layer of mesoderm begins. The edges of these two infolding sheets of tissue meet and fuse, forming a tube in the longitudinal axis of the embryo. This early intestine is attached through its entire length to the posterior wall of the embryo by the dorsal mesogastrium and is connected ventrally at its midpoint to the yolk sac. At this stage it is customary to distinguish three parts of the intestinal tract: (1) the foregut, which has a ventral as well as a dorsal mesentery; (2) the midgut, from which develop the lower part of the duodenum, the remainder of small intestine and the ascending and transverse colon, and (3) the hindgut, from which the remainder of the intestinal tract develops. For this study, only the midgut and hindgut need be considered.

The midgut increases in length, producing an anterior bend and a lengthened dorsal mesentery. The first part of the hindgut grows cephalad and, if not pulled upward, is anchored by a retention band of mesenchymal tissue which is described by Frazer and Robbins and by Dott, extending from the root of the superior mesenteric artery to the region of the splenic flexure. The upper part of the hindgut is then nearer the cephalic end of the embryo than is the first part of the midgut. The latter is depressed by the umbilical vein which is pulled downward across it by the enlarging liver. With the first part of the midgut depressed and the distal end anchored, rapid growth takes place. Due either to lack of intra-abdominal space or to a pull from the diminishing yolk stalk, the midgut is extruded into the coelomic cavity through the large umbilical opening. This extrusion is referred to as the embryologic or physiologic umbilical hernia (fig. 1), and is first seen between the 4 and the 10 mm. stage of the embryo. The midgut in the umbilical hernia lies outside the abdominal cavity proper and has no contact with other developing viscera. At approximately the 40 mm. stage of the embryo the intestines return to the abdominal cavity because of the pull exerted by the descending liver on the loops near the dorsal attachment, or because the change in pressure resulting from intra-abdominal enlargement sucks them back. After reentering the abdomen the intestines assume the general position seen at birth.

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42. Frazer, J. E., and Robbins, R. H.: On the Factors Concerned in Causing Rotation of the Intestine in Man, J. Anat. **50**:75 (Oct.) 1915.

43. Pernkopf, Eduard: Die Entwicklung der Form des Magen-Darm-Kanales beim Menschen, Ztschr. f. d. ges. Anat. **85**:1, 1928.

44. Hertzler, A. E.: The Peritoneum, St. Louis, C. V. Mosby Company, 1919.

45. Prentiss, C. W., and Arey, L. B.: A Laboratory Manual and Text-Book of Embryology, ed. 3, Philadelphia, W. B. Saunders Company, 1922.

During the existence of the umbilical hernia notable development in the blood vessels which supply the bowel takes place. Huntington stated that the main branches of the superior mesenteric artery are present during this stage. Pernkopf, in a detailed study, reported that the first identifiable branch of the superior mesenteric artery is the ileocolic in an embryo of 16.7 mm.; in an 18 mm. embryo the middle and left colic arteries are present, and in a 33.5 mm. embryo the vessels are present and are used to identify the parts of the colon.

The great omentum is in intimate relationship with the colon and its development deserves consideration. The embryologic development of the omentum as described by Arey, Hertzler, Huntington, Cunning-

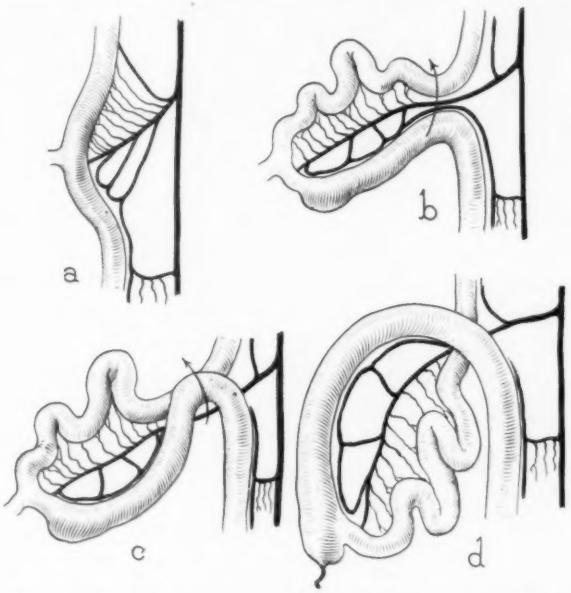

Fig. 1.—Embryologic hernia and rotation of the midgut.

ham, Piersol and Lockwood [46] is constant. The omentum develops from the dorsal mesentery of the stomach as that organ undergoes rotation to the left, descends and assumes a somewhat horizontal position between the 5 to 17 mm. stages of the embryo. The omentum forms a double layered, anterior wall for the lesser peritoneal cavity, and as it grows downward, it lies on the intestines as a flat bag with one lip attached to the greater curvature of the stomach and the other to the posterior abdominal wall.

46. Lockwood, C. B.: The Development of the Great Omentum and Transverse Mesocolon, J. Anat. & Physiol. **18**:257, 1883-1884; On the Development of the Arteries of the Abdomen and Their Relation to the Peritoneum, Proc. Roy. Soc. London **38**:485, 1884-1885.

In the tenth week of the embryo (38 mm.) the lower layers of the omentum pass to the posterior abdominal wall, leaving a fossa between the colon and the omentum. Later the fossa is obliterated and the lower layers of the omentum fuse with the peritoneal covering of the transverse colon. Pernkopf found the fusion present in an embryo of 63 mm., and Hertzler in an embryo of 11 cm. The main arteries of the colon having been formed before the return of the umbilical hernia to the abdominal cavity at about the 40 mm. stage of the embryo, there can be no arterial anastomosis between the omentum and the transverse colon other than through peritoneal branches.

The study of the embryologic development of the colon and omentum shows two important facts with reference to the blood supply: (1) the main arteries are developed while the greater part of the colon is outside of the abdominal cavity proper so that arterial anastomosis with these arteries is impossible, and (2) the fusion of the colon and the omentum takes place after the formation of the arteries of the colon so that nothing greater than a supply of peritoneal twigs can be expected from the omentum.

Anomalies.—Most anomalies of the arteries of the colon which have been reported affect the superior mesenteric artery near its origin and are, for that reason, consistent with embryologic development. Thus Aeby,[47] Fetterolf,[48] and Sobotta reported cases of a common origin of the celiac axis and the superior mesenteric artery, and Bühler,[49] Morris and others reported the occasional existence of an anastomosing branch between the celiac axis and superior mesenteric artery. Bühler's explanation of a common trunk for the two arteries during the early embryonic stages is adequate for both types of anomaly. Right or left or accessory hepatic arteries from the superior mesenteric arteries are reported by Wilson, Sobotta, Fetterolf, Cunningham, Henle and Gerrish. A double superior mesenteric artery has been reported by Delannoy,[50] Henle and Cunningham. These anomalies are consistent with embryologic development, as they deal with the superior mesenteric artery close to the origin. However, an anomaly such as Wilson reported, in which the middle colic artery is derived from the hepatic artery, is embryologically unsound.

The inferior mesenteric artery remains entirely within the abdominal cavity during embryologic development so that anomalous anastomosis

47. Aeby: Ein seltener Fall von Gefässanomalie, Cor.-Bl. f. schweiz. Aerzte **2**:120 (March 15) 1872.

48. Fetterolf, G.: Variations in the Arteries of the Human Body, Univ. Pennsylvania M. Bull. **21**:323, 1908-1909.

49. Bühler, A.: Ueber eine Anastomose zwischen den Stämmen der Arteria coelica und der Arteria mesenterica superior, Morphol. Jahrb. **32**:185, 1904.

50. Delannoy, Emile: Artère mésentérique supérieure double, Bull. et mém. Soc. anat. de Paris **93**:346 (April) 1923.

with adjacent arteries is possible. References to such anomalies are frequent. The entire failure of the inferior mesenteric artery, its place being taken by branches of the superior mesenteric artery, is reported by Cunningham, Henle, Merkel and Morris. Henle, and Jacques [51] reported anastomosis between the splenic and left colic arteries, and Henle reviewed three cases in which the middle colic artery was supplied by the splenic artery. Most modern anatomists do not refer to instances of anastomosis of the splenic and left colic arteries, and Fetterolf stated that he has never seen the splenic artery supply branches to the intestine. Anastomosis of the inferior mesenteric artery with hepatic, renal, suprarenal or gastric arteries has been reported, particularly by early modern anatomists. The fact that such anastomoses are not reported by later anatomists, with better injected specimens to dissect, casts some doubt on the early reports.

In this study, both the inferior and superior mesenteric arteries were found to exist as single branches in all specimens. In the series studied by the first method (removal and then injection with celluloid) arteries anastomosing with those of other viscera were not seen, but as the removal was rapid, there was no adequate opportunity to determine their presence. However, the second method of injecting opaque material into the distal end of the superior mesenteric artery severed immediately after the origin of the inferior pancreaticoduodenal artery gave an excellent opportunity to observe extraneous anastomoses. In no case were anastomosing arteries to adjacent organs observed, and no other viscera were found injected with the opaque material. This lack of anastomosis serves to verify the observation of Bellini [52] that variations in the mesenteric arteries are rare.

Arteries.—A simple description of the arteries of the colon is given by Piersol:

> The arteries of the colon are derived from the superior and the inferior mesenteric. The former supplies the caecum, the ascending and the transverse colon and a varying amount of the descending colon. The supply of the latter is completed by the inferior mesenteric which is also distributed to the sigmoid flexure. The general plan includes a series of anastomoses between neighboring branches, by which long arterial arches run near the border of the gut, to which they give off irregular twigs.

Following this general description, the blood supply of the colon may be divided into three parts, the main arteries, the anastomosing loops or marginal artery and the terminal arteries.

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51. Jacques, P.: Quelques anomalies artérielles, Bull. Soc. anat. de Paris **9**:252 (April) 1895.

52. Bellini: Observations et notes sur le trajet des artères, Bull. Soc. anat. de Paris **8**:696 (Oct.) 1894.

Main Arteries: In the "Basle Anatomical Nomenclature" [53] the arteries to the colon derived from the superior mesenteric artery are: ileocolic, right colic and middle colic, and from the inferior mesenteric, the left colic. Each of these arteries will be described separately.

The ileocolic artery is generally described as the last artery given off on the right side of the superior mesenteric artery and as one of its two terminal branches. The terminal branches of the ileocolic artery are designated: (1) a colic branch which ascends along the wall of the colon; (2) an ileac branch which continues downward and then to the left along the terminal portion of the ileum to anastomose with the last intestinal artery and enclose the avascular area of Treves; (3) an anterior cecal artery which courses downward to the anterior surface of the cecum; (4) a posterior cecal artery which passes to the posterior surface of the cecum, and (5) the artery to the appendix. In the extensive work of Kelley,[54] Deaver,[55] and Jonescu and Juvara,[56] on the arteries of this region, not only are five main branches of the ileocolic artery described, but the irregularity of the origin of these vessels is emphasized.

In every specimen of this study the ileocolic artery coursed to the right toward the ileocecal valve. The general course of the artery varied slightly with the position of the ileocecal valve, which in turn is dependent on the descent of the cecum before and after birth. The artery subdivides at a distance from the ileocecal valve varying from 2.5 to 9 cm., but in the majority of specimens the distance is about 6 cm. As a rule, the first branch to be given off by the ileocolic artery is the ascending colic (figs. 2 and 3), but one of the cecal branches may arise first (figs. 4 and 5). In some cases there are several ascending colic branches (figs. 6 and 7). In specimens in which the ileocolic artery divided at a considerable distance from the ileocecal valve, anastomosis between the branches sometimes occurred (fig. 4).

The artery to the appendix, although usually originating from the posterior cecal branch of the ileocolic artery, may be given off by one of the other branches, or may have an independent origin directly from the ileocolic artery. In one specimen the appendix is supplied by seven distinct branches from the posterior cecal and ileal arteries.

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53. Emmel, V. E.: The B N A Regional and Systematic Anatomy, Philadelphia, Wistar Institute Press, 1927.

54. Kelley, H. A.: The Vermiform Appendix and Its Diseases, Philadelphia, W. B. Saunders Company, 1905.

55. Deaver, J. B.: Appendicitis, ed. 4, Philadelphia, P. Blakiston's Son & Co., 1913, p. 56; Surgical Anatomy of the Human Body, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1927, vol. 3, p. 426.

56. Jonescu, Toma, and Juvara, Ernest: Anatomie des ligaments de l'appendice vermiculaire et de la fosette iléo-appendiculaire, Progrès méd. **19**:273; 303; 321; 353; 369, 1894.

In regard to the ileocolic artery, it may be concluded: (1) the existence of the artery is constant; (2) its course is toward the ileocecal valve and varies slightly with the position of the valve, and (3) the terminal branches of the artery vary in their origin.

The right colic artery is described as the second artery from the right side of the superior mesenteric artery. Its course is to the right, below the mesocolon to the region of the hepatic flexure of the colon. The right colic artery is the most inconstant of the colic arteries. Early

Fig. 2.—Posterior view of a specimen injected with opaque material showing: (1) the ascending colic artery as the first branch of the ileocolic artery; (2) the artery to the appendix from the ileocolic artery; (3) the absence of the right colic artery, and (4) failure of the marginal artery and anastomosis between the ileocolic and middle colic arteries.

anatomists, such as von Haller, failed to describe the right colic artery, and later Hyrtl and Henle refer to its presence by saying that two or three arteries to the colon come from the superior mesenteric artery. All modern anatomists and writers on surgical subjects describe the artery but call attention to a variable origin, either from the ileocolic or middle colic arteries. The absence of the right colic artery is given

an evolutionary background by Waldeyer,[57] who stated that in primates it was seen only once and then as a feeble branch in a gorilla. Waldeyer stated his belief that the artery should be named only when it has an independent origin from the superior mesenteric artery, and he found the independent origin to occur in about 50 per cent of cases. This view is evidently held by Fetterolf, who reported the absence of the artery in several cases. Hartmann [58] found this artery with an independent

Fig. 3.—Posterior view of celluloid cast of a specimen showing: (1) the ascending colic artery as the first branch of the ileocolic artery; (2) the origin of the right colic artery from the middle colic artery, and (3) the large ascending branch of the left colic artery with several branches to the marginal artery.

origin only once in fifteen subjects, and Lardennois and Okinczyc [59] described the disposition of three colic arteries from the superior

57. Waldeyer, H. W. G.: Die Kolon-Nischen, die Arteriae colicae und die Arterienfelder der Bauchhöhle, nebst Bermerkungen zur Topographie des Duodenum und Pankreas, Berlin, G. Reimer, 1900.

58. Hartmann, Henri: Traveaux de chirurgie anatomo-clinique, S. 3 Chirurgie de l'intestin, p. 125, Paris, G. Steinheil, 1907.

59. Lardennois, G., and Okinczyc, J.: La véritable terminaison de l'artère mésentérique supérieure. Deductions pathologiques, Bull. Soc. anat. de Paris **12**:13 (Jan.) 1910.

mesenteric artery as exceptional. Jamieson and Dobson,[60] in a series of more than thirty cases, found the right colic artery as a direct branch from the superior mesenteric artery in less than 50 per cent, as a branch of the ileocolic artery in about 30 per cent and as a branch of the middle colic artery in some others.

A consideration of the existence of the right colic artery becomes academic when a particular origin is insisted on before naming the artery. If there is a vessel from the superior mesenteric, middle colic

Fig. 4.—Specimen injected with opaque material showing: (1) the anterior cecal artery as the first branch of the ileocolic artery; (2) anastomosis between the branches of the ileocolic artery; (3) the origin of the right colic artery from the ileocolic artery, and (4) slight anastomosis between the ileocolic and right colic arteries.

or ileocolic artery that approximates the course of the right colic artery, which supplies the colon in the region of the hepatic flexure and anastomoses with the adjacent colic arteries, a right colic artery may be said to exist.

In the specimens studied the variations of the right colic artery were marked. The artery originated from the superior mesenteric in 40 per cent of the cases (figs. 4 and 7), from the middle colic in 30 per

60. Jamieson, J. K., and Dobson, J. F.: The Lymphatics of the Colon, Ann. Surg. **50**:1077 (Dec.) 1909.

cent of the cases (fig. 3), from the ileocolic in 12 per cent (fig. 6), whereas in 18 per cent there was no artery that corresponded in course or distribution to the right colic artery (fig. 2). Sometimes the right colic artery was small, and in these cases the deficiency was compensated for by large middle colic and ileocolic vessels. It may be concluded that the right colic artery is extremely variable in presence, origin and size.

The middle colic artery is described as the first artery coming from the right side of the superior mesenteric artery. It runs to the right

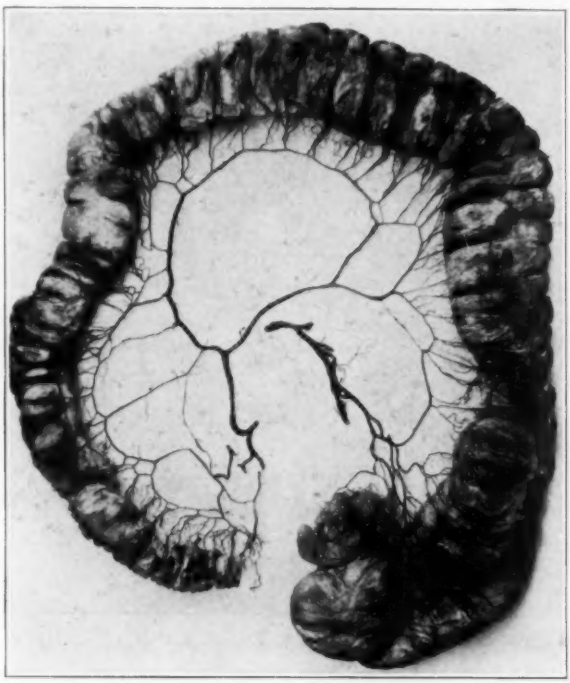

Fig. 5.—Posterior view of celluloid cast of a specimen showing: (1) the anterior cecal branch (broken) as the first branch of the ileocolic artery, and (2) the absence of the middle and right colic arteries, replaced by the left colic artery.

between the layers of the mesocolon, then divides, its branches supplying the transverse colon and anastomosing with the right and left colic arteries. Some remarkable variations of the middle colic artery have been reported. Sappey [61] stated that the middle colic artery is often absent. Henle described branches of the superior and inferior mesenteric arteries replacing the middle colic, and it is Hyrtl's belief that it

61. Sappey, M. P. C.: Traité d'anatomie descriptive; avec figures intercalées dans le text, ed. 3, Paris, V. A. Delahaye et Cie, 1876, vol. 2, p. 556.

may be replaced by omental branches. Henle reported a case of two middle colic arteries, and Waldeyer described an accessory middle colic artery occasionally arising before the middle colic artery and coursing to the left. Moynihan [62] occasionally found an accessory middle colic artery running directly toward the middle of the transverse colon, and Jamieson and Dobson [60] noted its occasional occurrence.

In this study, the variations of the middle colic artery were confirmed. The point of bifurcation of the artery was from 3 to 11 cm. from the wall of the colon, but usually it divided between 5 and 7 cm.

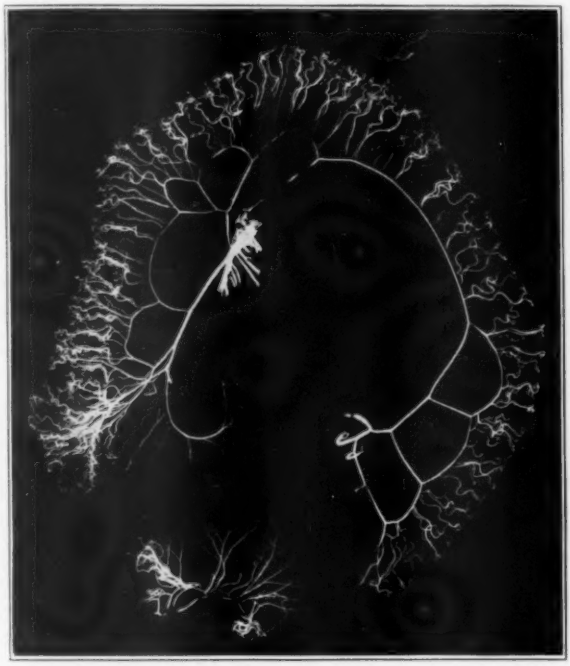

Fig. 6.—Specimen injected with opaque mixture showing: (1) the anterior cecal artery as the first branch of the ileocolic artery; (2) multiple ascending colic branches from the anterior cecal branch, and (3) the origin of the right colic from the ileocolic artery.

As a rule, the larger the artery and its branches, the greater the distance between the point of bifurcation and the wall of the colon. In all cases the artery began its course to the right, and usually only a part of one branch passed to the left of the median line of the body. Usually there were two branches of the middle colic artery (fig. 7), but trifurcation of the artery was not unusual (fig. 8) and as many as four

62. Moynihan, Berkeley: The Cavendish Lecture, Being Remarks on the Surgery of the Large Intestine, Lancet **2**:1 (July 5) 1913.

branches were sometimes found (fig. 9). In 27 per cent of the specimens a large branch of the middle colic artery ran toward the splenic flexure and reinforced the marginal artery near that point (figs. 9 and 10). In 10 per cent of the specimens an accessory middle colic artery was found arising from the superior mesenteric artery above the origin of the middle colic artery, running to the left in the mesocolon and anastomosing with the marginal artery near the splenic flexure (fig. 11). In two specimens (5 per cent of the series) the middle colic artery was entirely absent and was replaced by a large branch from the left colic artery (fig. 5).

Fig. 7.—Posterior view of a celluloid cast of a specimen showing: (1) the origin of the right colic from the superior mesenteric artery; (2) the middle colic artery dividing into two large branches, and (3) the left colic artery passing above the splenic flexure to the transverse colon.

It may be concluded that the middle colic artery does not occur constantly, that it varies in the number of branches, and through large branches, or by accessory middle colic arteries it supplies the left side of the transverse colon and splenic flexure in 37 per cent of the cases.

The left colic artery is described as the first branch of the inferior mesenteric artery. It passes transversely to the left and divides into an ascending branch and a descending branch which supply the descending colon and anastomose respectively with the left branch of the middle colic artery and the first sigmoid artery. There is some confusion among the older anatomists concerning the names applied to the left colic artery.

As late as 1844, Cruveilhier referred to two or three left colic arteries, and Sappey, in naming the left colic artery, preferred to call all other branches of the inferior mesenteric artery, hemorrhoidal branches. This confusion was probably a result of designating the sigmoid as part of the descending colon, and the variation in the number of sigmoid arteries.

In this study the left colic artery was present in every specimen. The distance of the point of bifurcation from the wall of the colon varied from 3 to 10 cm. The course of the artery and its branches was extremely variable: In 27 per cent of the cases the ascending branch

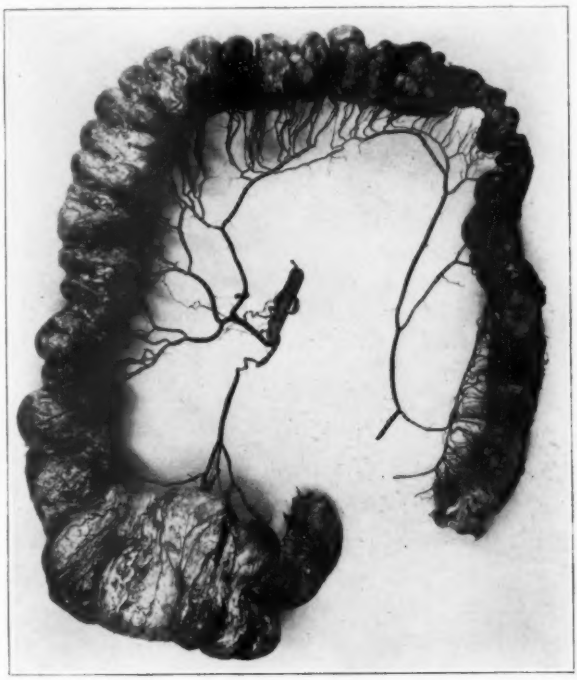

Fig. 8.—Celluloid cast of a specimen showing: (1) trifurcation of the middle colic artery and (2) anastomosis between the left and middle colic arteries effected by a slender branch.

did not extend to the splenic flexure (figs. 9 and 10), and in 63 per cent it passed above the flexure and supplemented the marginal artery in the region of the left transverse colon (figs. 7 and 8). In this last type of case the ascending branch was larger than the descending one and frequently had several branches connecting it with the marginal artery which lay close to the bowel (fig. 3). In these cases the ascending branch of the left colic artery served as a large and more distally situated second marginal artery. One specimen in which the mesocolon was "M" shaped had a large secondary anastomosing loop

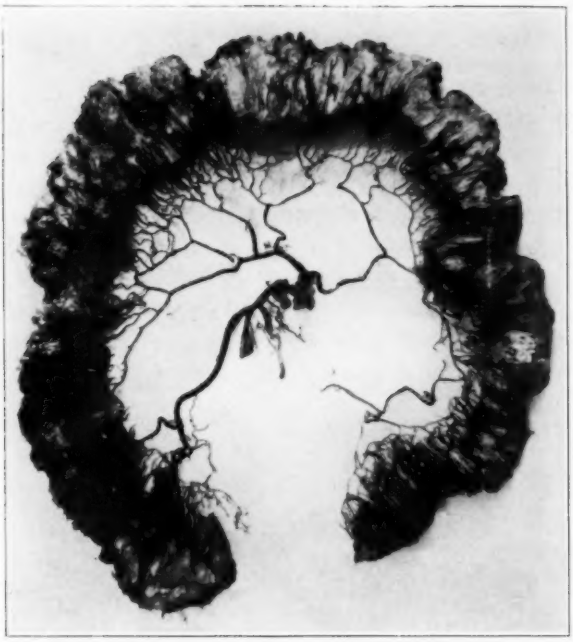

Fig. 9.—Celluloid cast of a specimen showing: (1) the middle colic artery with four branches; (2) the left colic artery going to the descending colon below the splenic flexure, and (3) a few tertiary loops along the marginal artery.

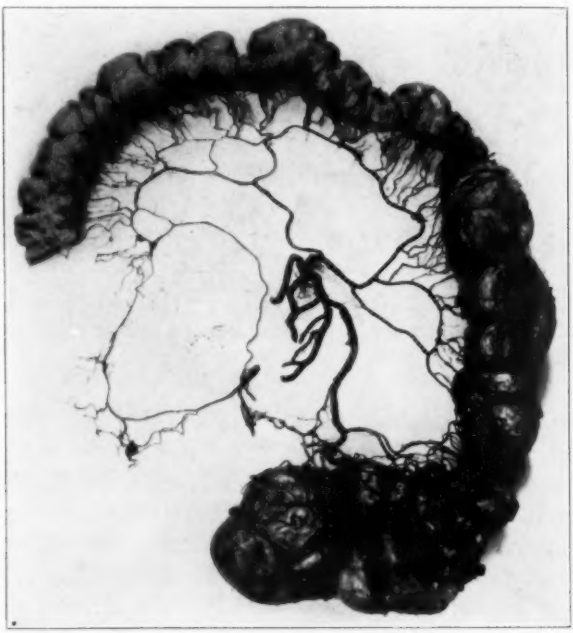

Fig. 10.—Posterior view of a celluloid cast of a specimen in which a branch of the middle colic courses toward the splenic flexure.

between the left and middle colic arteries and a smaller anastomosis between the left colic and superior mesenteric arteries (fig. 12). Both of these loops were short and sutured close to the base of the mesentery of the small intestine. The entire blood supply of the specimen was distorted by the deficiency in the mesocolon, although embryonic rotation appeared to have been normal.

It may be concluded that there is marked variation in the size, course and distribution of the branches of the left colic artery, and that

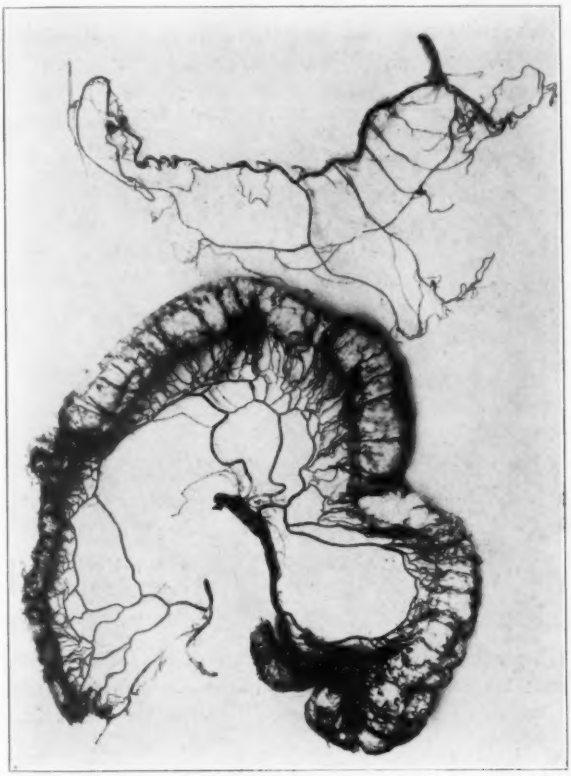

Fig. 11.—Posterior view of a celluloid cast of a specimen including injection of arteries of the omentum showing: (1) the accessory middle colic artery and (2) the left colic artery coursing to the descending colon below the splenic flexure.

in most cases the ascending branch extends above the splenic flexure to the transverse colon.

Marginal Arteries: The first comprehensive description of the blood supply of the colon by von Haller drew attention to the anastomosis of the adjacent colic arteries near the wall of the bowel. Since von Haller's description, anatomists have acclaimed the significance of the anastomosis along the wall of the colon as the only connection

between the superior and inferior mesenteric arteries. If the anastomosing loops are considered as an entity, the main colic branches may be considered simply as the source of supply for this artery.

Although the existence of the arterial arcade along the colon has long been recognized, descriptions by anatomists have been meager. This neglect may be due to the variations of the arcades. Von Haller stated that the arches are fewer and less often subdivided than in the small intestine, and that the trunks of the arches follow the course of the bowel. Cruveilhier described the structure as large arterial arches with their convexity near the bowel. Henle, Quain and Piersol only stated that the anastomosing branches run near the bowel. Gray placed

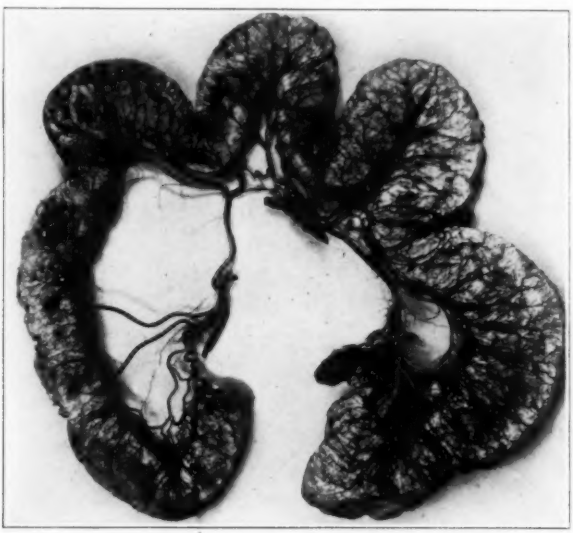

Fig. 12.—Posterior view of a celluloid cast of a specimen with "M" shaped transverse mesocolon showing secondary anastomosis between the left and middle colic arteries: *a*, small connecting branch between the left colic and superior mesenteric arteries.

the artery two fingerbreadths from the transverse colon. Hyrtl called attention to secondary and even tertiary arches in the angles of the flexures, and Jamieson and Dobson [60] stated that secondary and tertiary arches are not common.

Okinczyc [63] described multiple arcades at the angles of the colon and stated that they are more common at the splenic than at the hepatic flexure.

The continuity of the anastomosing arcades is not accepted unquestioningly. Okinczyc stated that the anastomosis between the arteries

63. Okinczyc, J.: Anatomine chirurgical des colons, in Hartmann, Henri.[58]

to the right and transverse portions of the colon is often slender. Merkel wrote that the anastomosis between the middle and left colic arteries may fail, and Cunningham, in considering the failure, called attention to the fact that in ruminants and some rodents there is no anastomosis between the mesenteric arteries. Among writers on surgical subjects, Lockhart-Mummery [64] mentioned occasional failure of anastomosis of the left and middle colic arteries.

With the growth of surgery, the significance of the anastomosis of the colic arteries has become more apparent. Litten,[65] in 1875, found that the anastomosis with the inferior mesenteric artery was not sufficient to prevent gangrene of the colon of dogs if the superior mesenteric artery was ligated. Morestin,[66] in 1893 (quoted by Archibald), reported that the inferior mesenteric artery in dogs might be ligated and circulation of the lower part of the bowel maintained. Archibald,[67] in 1908, substantiated the experiments of Morestin and also found that material injected into the superior mesenteric artery of cadavers would progress to the hemorrhoidal arteries when all branches of the inferior mesenteric artery were ligated some distance from the wall of the colon. Sudeck,[68] in 1907, studying the blood supply of the lower part of the colon by injection and roentgenologic examination, and Rubesch,[69] in 1910, writing on gangrene of the rectum after operations, drew attention to the importance of the artery running near the wall of the bowel. Drummond,[70] in 1913, presented evidence of the importance of the anastomosis of the colic arteries. In several postmortem investigations he tied all the main arteries of the colon and sigmoid near their origins, and found that the sigmoid vessels could be filled with material injected into the ileocolic artery. Drummond first used the term "marginal artery" in referring to the anastomosing arches along the wall of the colon. Rothschild [71] recently concluded, from animal experimentation, that severance of the mesentery of the

64. Lockhart-Mummery, Percy: Diseases of the Rectum and Colon and Their Surgical Treatment, London, Baillière, Tindall & Cox, 1923.

65. Litten, M.: Ueber die Folgen des Verschlusses der Arteria mesaraica superior, Virchows Arch. f. path. Anat. **63**:289 (May 25) 1875.

66. Morestin, quoted by Archibald.[67]

67. Archibald, Edward: Operative Treatment of Cancer of the Rectum, J. A. M. A. **50**:573 (Feb. 22) 1908.

68. Sudeck, P.: Ueber die Gefässversorgung des Mastdarmes in Hinsicht auf die operative Gangrän, München. med. Wchnschr. **2**:1314 (July 2) 1907.

69. Rubesch, R.: Ueber die Vermeidung der Darmgangrän bei Rectumoperationen, Beitr. z. klin. Chir. **67**:480, 1910.

70. Drummond, Hamilton: Some Points Relating to the Surgical Anatomy of the Arterial Supply of the Large Intestine, Proc. Roy. Soc. Med. (Sect. Proct.) **7**:185, 1914.

71. Rothschild, N. S.: Safety Factors in Mesenteric Ligations, Ann. Surg. **89**:878 (June) 1929.

large bowel which permits the marginal artery to be left intact does not interfere with the viability of the bowel. At present, in spite of the reported failures of anastomosis between the colic arteries and the protests of Desmarest,[72] and Jamieson and Dobson, surgeons successfully ligate individual colic arteries as the occasion demands and rely on vascularization through the marginal artery.

Study of the marginal artery in the injected specimens emphasized its value as a source of blood supply to the colon. The marginal artery was continuous from the ascending colon to the sigmoid in all but 5 per cent, and in these there was failure of anastomosis between the ileocolic and the right colic arteries (fig. 2). In several other specimens this anastomosis was slight (fig. 4); however, this appeared to be evidence of profuse supply to the part rather than of avascularity, as there were large, independent branches of the cecum and ascending colon.

In all of the specimens there was union of the left colic and middle colic arteries. This fact deserves particular emphasis because of the prevalent, hazy statements to the contrary. One of us (Dr. Rankin[73]) incorrectly wrote that the anastomosis occasionally fails to exist and this opportunity is taken to correct the statement. In more than a hundred specimens in which this particular area was examined there was no failure of anastomosis of the middle and left colic arteries. The only specimen which suggested this possibility was one (fig. 8) in which the left and middle colic arteries were large, and the anastomosis was affected by an unusually slender branch, which may have been the result of an artefact in the preparation or injection of the specimen.

The distance of the marginal artery from the wall of the colon is inconstant. A general estimate should not be made as the distance varies in each specimen, and in the different parts of the same specimen, from a fraction of 1 to 8 cm. As a rule, the artery is farthest from the wall at the points of bifurcation of the main arteries; the larger the marginal artery at a particular point, the more distant it is likely to be from the bowel. Usually the marginal artery is nearer the left half of the transverse and the descending portion of the colon than the right half of the colon.

The secondary arcades are also inconstant. They are most common at the points of bifurcation of the main arteries or their subdivisions, but there is no regularity in their presence. Tertiary loops are occasionally found, but never in the number or frequency suggested by

72. Desmarest, E.: Technique de la résection de l'angle gauche du colon pour cancer, J. de chir. **14**:575, 1917-1918.

73. Rankin, F. W.: Surgery of the Colon, New York, D. Appleton and Company, 1926.

Sharpe,[74] who described a dichotomous distribution of the arteries of the colon. Secondary loops give a more flexible blood supply to a colon, but their existence is not constant enough so that the surgeon may safely place any degree of reliance on them.

It may be concluded that a marginal artery occurs quite constantly, failing only in rare cases along the ascending colon in the presence of a profuse supply from direct branches; that it runs at varying distances from the wall of the colon, and that it may have secondary loops in different positions in its course.

Terminal: The terminal vessels of the colon have not been fully described. Von Haller gave one of the earliest and best descriptions: " . . . the branches on the intestines less arbuscular (than in the small intestine), divided at less angles and more tortuous; and the reticulation in the cellular substance is lower." Henle simply stated that the arches give direct branches to the colon without further anastomosis and the branches run in the haustra. Sobotta stated that a number of the branches irregularly anastomose before they enter the wall of the colon. Piersol described irregular twigs passing to the colon, and Gray and Cunningham stated that branches are distributed to the colon by the loops formed by the branches of the colic arteries.

The terminal arteries of the colon are not described by histologists. Bailey, Böhm,[75] Jordan, and Lewis and Stöhr[76] described the vessels after they enter the intestinal wall but did not mention their course proximal to that point.

The terminal arteries of the colon have been most thoroughly described by surgeons. Drummond,[77] writing on diverticula of the colon, Meillere[78] on the epiploic appendages, and Fischer,[79] looking for cause of gangrene in operating on the colon, fully described the course of these arteries. Eisberg[80] called attention to the difference in

74. Sharpe, N. W.: The Arcuate Distribution of Arteria Mesenterica Superior and Arteria Mesenterica Inferior: Surgical Significance in Intestinal Resections, Interstate M. J. **20**:1152 (Dec.) 1913.

75. Böhm, A. A.: Text-Book of Histology, Philadelphia, W. B. Saunders Company, 1900.

76. Lewis, F. T., and Stöhr, Philipp: A Text-Book of Histology, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1913.

77. Drummond, Hamilton: Sacculi of the Large Intestine, with Special Reference to Their Relations to the Blood Vessels of the Bowel Wall, Brit. J. Surg. **4**:407, 1917.

78. Meillere, J.: Étude de la vascularisation des tuniques du segment gauche du colon et ses applications chirurgicales, Ann. d'anat. path. **4**:867 (Nov.) 1927.

79. Fischer, A. W.: In wie weit ist durch die Ablösung des Dickdarmfettbehanges der Sicherheit der Dickdarmnaht gefährdet? Arch. f. klin. Chir. **152**:638, 1928.

80. Eisberg, H. B.: On the Viability of the Intestine in Intestinal Obstruction, Ann. Surg. **81**:926 (May) 1925.

position of the vasa recti as they pierce the wall of the small intestine and of those that pierce the wall of the colon.

The branches of the terminal arteries usually originate independently from the marginal artery and proceed directly to the colon, but occasionally two branches may have a common origin. Anastomosis between terminal branches before they reach the colon is rare. Terminal arteries are most numerous in the cecum and ascending colon. The size of the terminal arteries in the transverse and descending colon is slightly smaller, and the number of vessels per centimeter is less than in the ascending portion. The branches vary slightly with the size of the subject, but there is no difference in the size of the arteries in the dilated and the contracted portions of the colon in the same specimen.

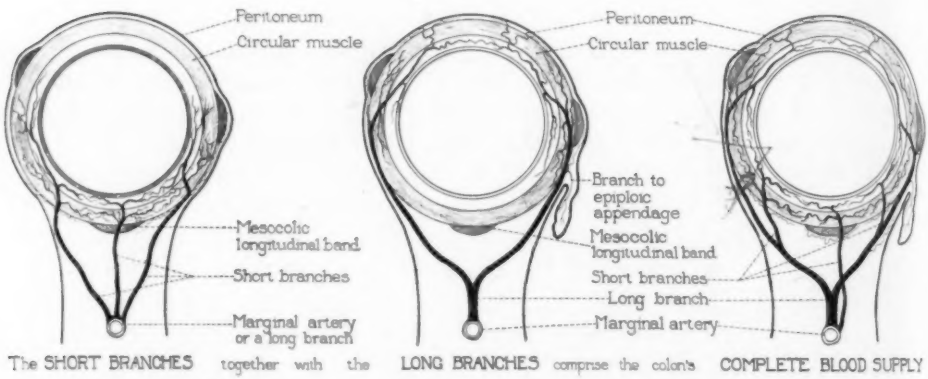

Fig. 13.—Diagram of the terminal arteries of the colon; *a*, long branches; *b*, short branches, and *c*, complete supply by both long and short branches.

The terminal arteries to the colon are of two types: long and short branches, a combination of the two types affecting the complete supply to the wall (fig. 13). The long branches divide near the mesocolic taenia, one branch courses in the haustra on the anterior aspect, and the other on the posterior aspect of the wall of the colon. In this part of their course the arteries lie in the serosa and give off short branches to the mesocolic portion of the colon, small twigs to the serosa and peritoneum and arteries to the epiploic appendages.

Near the amesocolic or distal longitudinal bands the long branches divide and pass deeply beneath the longitudinal muscle and through the circular muscle to the submucosa. In this position they continue their course, sending small branches upward to the muscle and peritoneal covering. In the submucosa anastomosis is established with the short branches and a relatively scanty anastomosis with the long branch from the opposite side of the colon (fig. 14).

The short branches of the terminal arteries to the colon may originate from the marginal artery, but the majority are given off by the long branches. The short arteries are smaller and about four or five times as numerous as the long branches. The first short branches to arise pierce the mesocolic longitudinal band, giving twigs to serosa and muscle in passing, and go directly to the submucosa. The other short branches lie loosely in the serosa where they appear tortuous and anastomose through fine serosal twigs. The branches then pass through the circular muscle to the submucosal plexus at various points. The large number of short branches gives the mesocolic arteries of the colon a preponderance of the blood supply. The general course

Fig. 14.—Dissection of a long terminal artery to the colon showing: (1) vessels to the serosa and epiploic appendage; (2) the long artery coursing through the circular muscle and beneath the amesocolic longitudinal band to divide in the submucosa, and (3) the submucosal anastomosis with the vessels from the opposite side of the colon.

of the terminal arteries to the colon is perpendicular to the axis of the bowel with little lateral anastomosis. This arrangement is obvious in roentgenograms of a segment of colon injected with opaque material. When an injected segment of colon is compared with a segment of injected jejunum from the same case, more acute angulation and profuse lateral anastomosis of the arteries in the wall of the small bowel are seen.

Regarding the terminal arteries of the colon, it may be concluded that: (1) they are of two types, long branches which supply the amesocolic or distal third of the colon, and short branches which supply the mesocolic or proximal two thirds of the colon; (2) the mesocolic taenia

portion of the colon has most of the blood supply; (3) the course of the terminal arteries is in general perpendicular to the axis of the bowel, and (4) there is little anastomosis between the terminal vessels except in the submucosa.

Arterial Pattern.—The blood supply of the colon, composed of the main colic arteries and the marginal artery, should now be considered. An interesting variety of patterns was found in the specimens, no two of which were alike. The arteries and their branches varied in size and distribution. They were usually unequal and supplied lengths of the colon corresponding to their size. When one artery was large, the adjacent arteries were likely to be smaller than normal. Because of branches from the middle colic artery passing to the left, the existence of an accessory middle colic artery in 10 per cent of cases and the frequency with which the left colic artery passes above the splenic flexure, the long single arcade customarily described as the anastomosis between the middle colic and left colic arteries is usually reduced in length.

A substantiation of the varying distribution of the colic arteries is supplied by postmortem observations in cases of thrombosis of the mesenteric vessels. Trotter [81] reviewed two cases of complete occlusion of the inferior mesenteric artery, in both of which the entire descending colon was involved. Contrasted with these two cases was one reported by Parker [82] in which there was complete occlusion of the inferior mesenteric artery with gangrene beginning in the lower half of the descending colon. Similarly, the extent of intestinal involvement varied in complete thrombosis of the superior mesenteric artery. Trénel [83] and Cénac reported involvement of the entire colon in complete thrombosis of the superior mesenteric artery, and Frank [84] observed that exploration in such cases may reveal the entire large intestine to be gangrenous. Compared with these observations is a recent case at the Mayo Clinic [85] in which there was complete occlusion of the superior mesenteric artery and a sharp line of demarcation at the hepatic flexure with viable intestine beyond this point. The only conclusion possible from a review of these cases is that the arteries supplied varying lengths of colon.

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81. Trotter, L. B. C.: Embolism and Thrombosis of the Mesenteric Vessels, New York, Cambridge University Press, 1913.

82. Parker, C. B.: Mesenteric Thrombosis with Report of Two Cases, Canad. M. A. J. **12**:655 (Sept.) 1922.

83. Trénel and Cénac: Thrombose de l'artère mésentérique supérieure, Bull. et mém. Soc. anat. de Paris **92**:406 (Nov.) 1922.

84. Frank, Louis: Mesenteric Vascular Occlusion: Report of Three Cases in Children, Am. J. Surg. **37**:304 (Dec.) 1923.

85. Steward, J. A.: Unpublished data.

ANASTOMOSIS OF ARTERIES BETWEEN THE OMENTUM AND COLON

Von Haller described the omental as well as the intercostal, lumbar and spermatic arteries as furnishing small arteries to the colon. A century later Hyrtl [16] emphasized the idea of anastomosis between the vessels of the colon and omentum when he found that material injected into the gastro-epiploic arteries filled the middle colic artery. He concluded that the anastomosis of the omental arteries with those of the colon might replace an absent middle colic artery. Later, Cruveilhier, Gray, Cunningham and Piersol stated that the transverse colon receives its blood supply from the omental arteries.

Surgeons have not verified the anastomosis between the arteries of the omentum and those of the colon. Lardennois and Okinczyc [59] stated that twigs do not exist which merit a ligature when the omentum is separated from the colon, and W. J. Mayo [86] found that only one artery near the splenic flexure need be tied in separating the two structures. Lardennois [87] pointed out that all important vessels of the omentum run on the anterior layer.

It has been shown that in the embryonic state the vessels of the colon have been formed before the omentum fuses to the transverse colon. Because of this fact and the discrepancy between surgical and anatomic observations, particular effort was made in this study to determine the amount of anastomosis between the vessels of the omentum and the colon. The omentum was left attached to the colon in all injected specimens. In two specimens used for injection of celluloid the gastro-epiploic arteries were carefully prepared and injected with a different colored celluloid solution for several hours before the superior mesenteric artery was injected.

The specimens we injected for roentgenologic study disclosed only occasional small branches in the attached omentum, although other arteries of very small caliber were well injected. In the series of injections of celluloid the omental arteries did not fill, and twigs longer than those to the peritoneum were not seen. In the two specimens in which the gastro-epiploic arteries were injected, two small branches were seen connecting the transverse colon with the omentum. The anterior arteries of the omentum became very small near the free edge, and although anastomosis between the small posterior arteries of the omentum and the terminal arteries to the colon is established, the connecting vessels were found to be peritoneal twigs from the long branches of the terminal arteries (fig. 11).

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86. Mayo, W. J.: Radical Operations for the Cure of Cancer of the Second Half of the Large Intestine, Not Including the Rectum, J. A. M. A. **67**:1279 (Oct. 28) 1916.

87. Lardennois, G.: Colectomie totale et colectomie sous-caecale. Technique opératoire, J. de chir. **12**:701, 1914.

It may be concluded that the anastomosis between the arteries of the omentum and the transverse colon is normally through a few branches from the terminal arteries of the colon, and that the anastomosing branches are about equal in size to large peritoneal twigs.

Veins.—As a corollary of the arterial circulation, it would be well at this point to describe the venous return of the blood from the colon. Early in our study special attention was given to veins of the colon, and a celluloid cast was made of both the arteries and veins, red and blue coloring material, respectively, being used in the two systems. Unfortunately, the large veins were difficult to fill and were broken in the attempt to photograph the resulting specimen.

It may be stated in general that the veins of the colon follow directly the course of the corresponding arteries. The left colic vein is an exception to this and will be considered later. The small veins from the wall of the colon to the marginal vein are of two types, the short and the long, as in the case of the arteries. Their general course is the same as that of the arteries, but there are always at least two veins for each artery. Whether this is a result of a physiologic demand due to absorption of liquid in the colon, or to the fact that the thin-walled veins are easily compressed by peristaltic movements of the colon so that more are needed, is a matter of conjecture.

The marginal vein of the colon follows closely the marginal artery in its formation and distribution, lying as a rule posterior and slightly mesial to the artery. From the marginal vein the subdivisions and principal branches parallel the course of the arteries, which form the general pattern, and empty into the superior mesenteric vein.

The left colic vein is a distinct exception to this orderly return of the colic veins along the arterial courses. It is formed by branches corresponding to the divisions of the left colic artery and unites with the inferior mesenteric vein. This union is lateral to the point of division of the arteries and the vein takes an upward course for several centimeters before curving mesially above the jejunoduodenal juncture to empty into the superior mesenteric vein. The termination of the inferior mesenteric vein is said to be often into the splenic vein; however, the opening is so close to the superior mesenteric vein that for all practical purposes this may be considered its termination.

Summary.—In studying the blood supply of the colon we removed the entire colon with its vessels and peritoneal attachments. The arteries of the specimens were injected with celluloid mixture and corroded, or with an opaque material and roentgenograms made. The vessels of forty such specimens were observed. The inferior and superior mesenteric arteries were always present and do not appear to anastomose with arteries of other viscera. The colic arteries vary in course, branching and distribution. The marginal artery is constantly

present, but runs at varying distances from the wall of the colon. The terminal arteries of the colon pursue a course different from those of the small intestine, are of two types, have little lateral anastomosis and furnish the mesocolic taenia portion of the colon more profusely than the distal part. There is only slight peritoneal anastomosis between the omentum and the transverse colon.

THE SIGMOID

Continuing downward, the descending colon becomes the sigmoid or pelvic colon. The exact point of transition is differently stated, either opposite the crest of the ilium or at the upper border of the psoas muscle. The structure of the bowel does not vary from that of the descending colon, although the diameter may be greater or smaller. This part of the large bowel is usually attached by a mobile mesentery or mesosigmoid to the posterior wall. Treves found that the length of the sigmoid varies from 15 to 71 cm., averaging 43 cm., and that the mesosigmoid is 7 cm. in length at the base and is from 10 to 20 cm. in width.

The arteries to the sigmoid usually arise from the lateral aspect of the inferior mesenteric artery and spread fanlike in the mesosigmoid toward the bowel (fig. 15), supplying not only the sigmoid, but in cases in which the left colic artery is small or has a high course, the lower part of the descending colon as well. The number of sigmoid arteries varies; Rubesch stated that there may be from one to nine and Pope and Judd, one to four. Drummond [88] found that the first sigmoid artery was given off by the left colic artery in more than 50 per cent of twenty cases studied, and it is not unusual to find all of the sigmoid branches arising from this vessel. The arteries divide and may undergo several subsequent subdivisions before reaching the marginal artery. The arterial branches anastomose with those in their vicinity to form a network in the mesosigmoid, ramifying the marginal artery. Pope and Judd called attention to these variations of arterial pattern in the mesosigmoid. There may be as many as four arcades in the arterial pattern of the sigmoid, and the number of vascular arches is apparently independent of the length and mobility of the mesosigmoid. The marginal artery, which is continuous with that of the descending colon, may lie from a fraction of a centimeter to several centimeters from the sigmoid wall. The distance of the marginal artery from the wall, as in the case of the colon, has no relation to the length of the mesosigmoid.

From the marginal artery of the sigmoid the terminal arteries are sent to the wall of the bowel. These are similar in kind (long and

88. (*a*) Drummond, Hamilton: The Arterial Supply of the Rectum and Pelvic Colon, Brit. J. Surg. **1**:677, 1914. (*b*) Drummond.[70]

short) and course to those of the colon. Frequently in the lower portion of the sigmoid and sometimes in the middle portion the longitudinal fibers spread outward from the longitudinal bands and form a complete investment of the bowel. In such cases the long arteries pass beneath the longitudinal fibers near the mesosigmoid portion of the bowel. The veins follow the general course of arteries in all the smaller ramifications until the large veins are formed. These take an upward course, uniting near the base of the mesosigmoid, finally joining with the left colic from the inferior mesenteric vein.

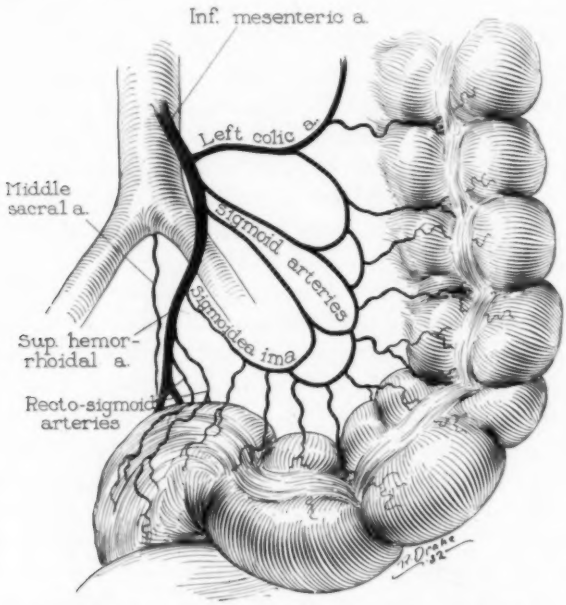

Fig. 15.—Arteries to the sigmoid and rectosigmoid.

THE RECTOSIGMOID

The portion of the large intestine at the juncture of the sigmoid and rectum has long been of particular anatomic and surgical interest, both as regards the bowel and its blood supply. In this region the longitudinal bands of muscle spread to form a complete coat; the mesosigmoid is at first markedly shortened, and a few centimeters farther it disappears entirely, leaving the bowel with peritoneum on the anterior surface only. In the last few decades this region has been referred to as the rectosigmoid, and although the term is anatomically descriptive, it is necessarily loosely used because of the variation in position and length of the two parts involved. The point at which the sigmoid ends and the rectum begins has been widely discussed. Gibson,[89] in 1697,

89. Gibson, quoted by Jones.[99]

said: "This hath its beginning at the first vertebra of the os sacrum." Treves, in 1885, located the beginning of the rectum opposite the third sacral vertebrae and assigned the upper portion to the pelvic colon. Jonnesco,[90] in 1889, confirmed Treves' observations, and since then anatomists for the sake of exactness have adopted the third sacral vertebra as a convenient landmark for defining the upper end of the rectum. In texts on surgery of the rectum writers are in the habit of quoting different figures as to the length of the rectum. Yeomans,[91] and also Edwards,[92] stated that the rectum is from 12 to 15 cm. in length; Pennington[93] gives the length of from 13 to 16 cm.; Cripps[94] from 15 to 20 cm., and Tuttle[95] from 9 to 15 cm. The length is greater in males than in females, greater in the aged than in the young, and it may be increased at any time by distention. Other methods of determining the upper limit of the rectum are also inexact. Gant[96] uses the third, or O'Beirne's sphincter, to define the juncture of the rectum and sigmoid, but Symington[97] doubted the existence of such a structure, and Hyrtl,[98] although believing in the sphincter physiologically, was often unable to demonstrate it in carefully executed dissections. Again, attempts have been made to determine the upper limit of the rectum by means of Houston's valves. Jones,[99] as well as Patterson,[100] advocated the use of the third valve of Houston, or the superior rectal fold, as the upper limit of the rectum. These folds are admittedly variable in form and position and are of no value as landmarks except when seen through a proctoscope.

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90. Jonnesco: Note sur l'anatomie de l'iliaque, Bull. Soc. anat. de Paris **3**:232 (March) 1889.

91. Yeomans, F. C.: Proctology, New York, D. Appleton and Company, 1929.

92. Edwards, F. S.: Diseases of the Rectum, Anus and Sigmoid Colon, ed. 3, London, J. & A. Churchill, 1908.

93. Pennington, J. R.: A Treatise on the Diseases and Injuries of the Rectum, Anus and Pelvic Colon, Philadelphia, P. Blakiston's Son & Co., 1923.

94. Cripps, W. H.: On Diseases of the Rectum and Anus, London, J. & A. Churchill, 1913.

95. Tuttle, J. P.: A Treatise on Diseases of the Anus, Rectum and Pelvic Colon, New York, D. Appleton and Company, 1906.

96. Gant, S. G.: Diseases of the Rectum, Anus and Colon, Philadelphia, W. B. Saunders Company, 1923.

97. Symington, J.: Further Observations on the Rectum and Anal Canal, J. Anat. & Physiol. **46**:289 (April) 1912.

98. Hyrtl, Joseph: Lehrbuch der Anatomie der Menschen mit Rücksicht auf physiologische Begründung und praktische Anwendung, Vienna, Wilhelm Braumüller, 1889.

99. Jones, F. W.: The Delimitation of the Rectum and Its Subdivisions, Proc. Roy, Soc. Med. (Surg. Sect.) **4**:85, 1911.

100. Patterson, A. M.: The Form of the Rectum, J. Anat. & Physiol. **43**:127 (Jan.) 1909.

Not only is it difficult to establish the upper limit of the rectum, but also that of the sigmoid, which varies in its position. The study by Bourcart [101] of the sigmoid of children gives a developmental background for the varying positions noted by practically all anatomists. Treves called attention to the frequency of morbid contractions and adhesions of the mesosigmoid, and Sappey warned [20] observers that the direction of the sigmoid presents many variations. Buie [102] called attention to the frequency with which the opening into the sigmoid is seen through the proctoscope to be on the right rather than the left side. From a review of the anatomic peculiarities of the region, we concluded that the point at which the sigmoid joins the rectum may vary appreciably in length.

Below the level of the left common iliac artery, the inferior mesenteric artery, lying in the base of the mesosigmoid, becomes the superior hemorrhoidal artery. The artery proceeds toward the median line and downward to its point of bifurcation. The point of bifurcation is generally said to be at the third sacral vertebra and is one of the criteria used to determine the upper end of the rectum. However, the point of bifurcation is in some dispute. Cripps found that the artery divides from 10 to 11 cm. above the anus, whereas Rubesch gives the point of division at from 17 to 20 cm. from the anus. Lockhart-Mummery's observation that the point of division of the superior hemorrhoidal artery varies considerably, as a rule at the upper end of the rectum, but that it is not rare to find a low bifurcation, seems most logical.

The branches of the superior hemorrhoidal artery in its short course from its beginning at the level of the left common iliac artery to its bifurcation have been extensively studied. In the ordinary case the branches generally consist of a vessel which sends a branch upward along the pelvic sigmoid to anastomose with the last sigmoid artery and several (from two to four) branches which run downward more or less parallel with the bowel.

Because of the mechanical difficulties encountered in this region and the frequent occurrence of gangrene following surgical procedures, the anastomosing artery from the superior hemorrhoidal to the sigmoid has commanded considerable attention. Numerous studies of the vessel have been made by injection. Sudeck, in 1907, was the first to emphasize the anastomotic value of the vessel. He found that the vessels of the rectum became filled with injected material from the inferior mesenteric artery by traversing the marginal artery when a ligature was placed on the superior hemorrhoidal artery above the origin of the

101. Bourcart, quoted by Tobias, Milton: Sigmoid Flexure in Constipation in Children: Preliminary Report, Am. J. Surg. **13**:301 (Aug.) 1931.

102. Buie, L. A.: Proctoscopic Examination and the Treatment of Hemorrhoids and Anal Pruritus, Philadelphia, W. B. Saunders Company, 1931, p. 45.

last branch to the sigmoid. If the ligature were placed below the origin of the artery, few if any of the rectal vessels were injected. Sudeck therefore established the origin of the last sigmoid artery as the critical point for maintaining the blood supply to the rectum in cases in which it was necessary to ligate the superior hemorrhoidal artery to obtain mobility. This experiment was substantiated by Hartmann [28] two years later. However, Rubesch, in 1910, studying this region by the same method, called attention to the fact that the last sigmoid artery, which he calls the sigmoidea ima, may be given off below the bifurcation of the superior hemorrhoidal artery, and that the so-called critical point is not exactly situated but may be encountered within a range of from 13 to 20 cm. from the anus. Manasse [103] emphasized the feebleness of the border vessel in the lower portion of the sigmoid and stated that the last sigmoid artery does not participate in it to a great extent. Drummond,[104] in 1914, studied by injection and roentgenograms the inferior mesenteric artery of twenty specimens. The results of this work are convincing. In eight of the cases the last sigmoid artery and its proximal anastomosis were very small, and in two cases the artery was not even present. The examples of carefully injected specimens in the articles of Pope and Buie,[105] and Pope and Judd confirm the variation in position and number of vessels in this region.

Thus, a review of the anatomy of the region of the rectosigmoid forces on us a realization of its variability, both in the bowel itself and in its attendant supply of blood. W. J. Mayo,[106] in an anatomic consideration of this region, showed that in 80 per cent of a series of specimens examined, there was distinct narrowing and longitudinal mucosal folds in the terminal part of the sigmoid. This he termed the rectosigmoid. A relationship of the length of this narrowed portion of the bowel and the distribution of the arteries to it, seems probable, but has not been demonstrated.

The vessels of this region have been studied by methods of injection. Because of extensive experience in this type of work, we deem it advisable to place certain limitations on the results of the method. Jamieson and Dobson [107] have expressed similar views. As a means of studying the course, the relationship and anastomosis of vessels and of

103. Manasse, Paul: Die arterielle Gefässversorgung des S. romanum in ihrer Bedeutung für die operative Verlagerung desselben, Arch. f. klin. Chir. **83**:999, 1907.

104. Drummond.[88a]

105. Pope, C. E., and Buie, L. A.: A Description of the Arterial Blood Supply of the Pelvic Colon, Tr. Am. Proct. Soc., 1929, p. 78.

106. Mayo, W. J.: A Study of the Rectosigmoid, Surg., Gynec. & Obst. **25**:616 (Dec.) 1917.

107. Jamieson, J. K., and Dobson, J. F.: The Lymphatics of the Colon, Proc. Roy. Soc. Med. (Surg. Sect.) **2**:149, 1909.

preserving a permanent record of the specimen, the various methods of injecting the arteries are satisfactory. However, it is impossible as well as dangerous to draw conclusions regarding the vascular potentialities of these same vessels during life. The methods have many variable factors. The postmortem contraction of smooth muscle is neither understood nor governable; the extent of the postmortem clotting and the degree of thoroughness with which the vessels are cleansed by different investigators will alter the results, and finally the type of material used for injection and the amount of pressure maintained within the system will alter the extent and valuable qualities of the anastomosis present. It is obvious that although injection of a mesenteric artery will fill the branches of the entire intestinal tract, the suggestion made by one observer that circulation could be maintained by the inferior mesenteric artery after ligation of the superior mesenteric artery is not warranted. Similarly, the evidence of extensive pelvic anastomosis through small vessels after the injection of the inferior mesenteric artery with mercury does not mean that a rectal stump would be preserved from gangrene after ligation of the superior hemorrhoidal artery, as claimed by another observer.

In any deductions from specimens in which the arteries have been injected, it must be remembered that we are drawing conclusions from arteries which have been completely relaxed and stretched by constant internal pressure usually greatly in excess of normal blood pressure. Thus a sclerosed vessel may be distended until its channel is much larger than normal, the exact reverse of the condition during life. Since many patients who are operated on for disease of the colon and rectum are of advanced age with more or less arteriosclerosis, we believe that attempts to draw inferences concerning the blood supply during life from injected specimens should be made with the greatest conservatism.

THE RECTUM

The rectum is supplied by a variable number of small arteries from the superior hemorrhoidal artery before its division, by the right and left branches of the superior hemorrhoidal artery, by the middle and the inferior hemorrhoidal arteries and by a variable amount from the middle sacral artery.

For many years anatomists have described the arterial supply of the upper part of the rectum as coming only from the right and left branches of the superior hemorrhoidal artery. Quénu,[108] in 1893, described a branch from the superior hemorrhoidal artery above its division coursing upward and anastomosing with the last sigmoid

108. Quénu, E.: Des artères du rectum et de l'anus chez l'homme et chez la femme, Bull. Soc. anat. de Paris **7**:703 (Dec.) 1893.

artery. Later Rubesch described rami of the superior hemorrhoidal artery to the bowel which are given off above the bifurcation and which do not anastomose. Drummond [88] noticed one or two encircling branches, with little anastomosis above or below, given off from the superior hemorrhoidal below the last sigmoid artery. Pope and Buie demonstrated that these vessels are constantly present in varying numbers and that they have some anastomosis with the adjacent arteries. These small vessels supply the bowel in the gap between the termination of the marginal artery in the lower portion of the sigmoid and the division of the superior hemorrhoidal artery (fig. 15). Their course is at once encircling toward the anterior aspect of the bowel and downward, coursing more or less parallel with the longitudinal axis of the rectum on its lateral and anterior aspect. The vessels vary in number from one to five and both number and size are proportional to the anatomic variations encountered in this region, that is, a high, small or absent last sigmoid artery, or a low dividing superior hemorrhoidal artery. They are to be regarded as supplemental and irregular vessels.

The superior hemorrhoidal artery divides near the upper end of the rectum into two branches, a right and a left superior artery (fig. 16). The point of bifurcation is not constant but usually is opposite the second or third sacral vertebra and, in many instances, is marked by absence of the mesosigmoid. Pope and Judd found that the point of bifurcation is 18 cm. from the origin of the inferior mesenteric artery. The branches course downward along the rectum, gradually encircling it from the posterior aspect. The two branches are seldom equal in size. Quénu,[108] in a meticulous study of the arteries in thirteen specimens, found that the right branch is usually the larger, and frequently furnishes a large branch to the posterior surface of the rectum. Branches of the arteries are given off irregularly to pierce the thick musculature of the rectum at an acute angle and ramify in the submucosa. Among the lowest branches are some which anastomose with the middle hemorrhoidal and prostatic or vaginal arteries.

The middle hemorrhoidal arteries are the first vessels to the large bowel to be derived from outside the splanchnic circulation. Their origin is variable, coming either directly from the anterior division of the internal iliac artery, or from a common trunk with the middle vesical, vaginal, prostatic or internal pudic artery. The arteries course forward to the lateral aspect of the rectum along which they descend, sending into it small irregular branches, some of which anastomose with the branches of the superior hemorrhoidal and some with the vaginal, vesicle or prostatic arteries. The middle hemorrhoidal vessels are inconstant in size, distribution and anastomosis. Particular interest has been centered on the anastomosis of the middle with the superior hemorrhoidal artery. Drummond [104] encountered a case in which there

were no middle hemorrhoidal arteries, and Quénu [108] in his more detailed study found the anastomosis extremely irregular. In the thirteen cases examined by Quénu,[108] there was complete failure of anastomosis between the middle and superior hemorrhoidal arteries in one case, the anastomosis was through one side only (most frequently the left) in eleven cases, and was bilateral only once.

It must be concluded, therefore, that although the middle hemorrhoidal artery usually anastomoses with the superior hemorrhoidal

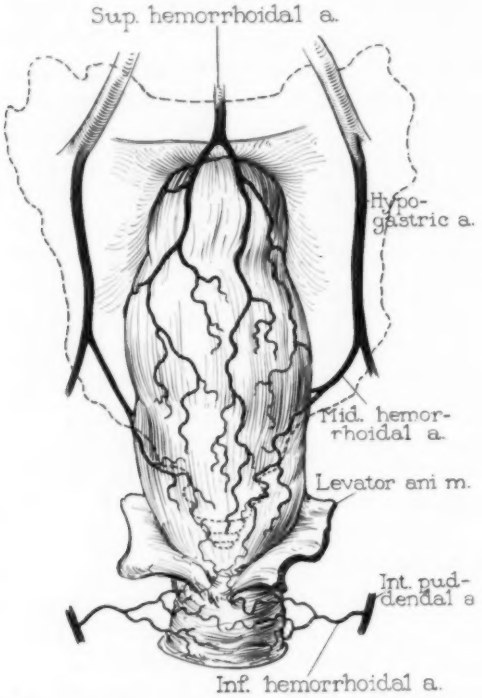

Fig. 16.—Arteries to the rectum (posterior view).

artery as well as with the vesical and prostatic or vaginal vessels, the relationship is not constant and no great reliance can be placed on it surgically.

The last artery to the large bowel is the inferior hemorrhoidal. These arteries, usually one on each side, arise from the internal pudic artery during its course through Alcock's canal in the perineum. The vessels subdivide irregularly into three or four smaller branches which circle the anus anteriorly and posteriorly. The vessels supply the musculature of the anus and by fine twigs anastomose with the middle hemorrhoidal artery.

In specimens of the rectum in which the arteries are carefully injected, an anastomosis with the middle sacral artery is seen. This small vessel originates at the bifurcation of the aorta and descends along the anterior surface of the sacrum. Quénu [108] particularly has noted this vessel, and found that it furnishes two or three small branches directly to the posterior wall of the rectum. Pope and Buie included it in the retrorectal plexus. The artery is small, its branches are inconstant and its value as a supply to the rectum is negligible.

The veins of the rectum have received considerable attention from anatomists because of the anastomosis between the portal and caval systems. The rectal veins correspond in name, number and general course to the arteries. The inferior hemorrhoidal veins drain the region of the anus and sphincter and communicate not only with the middle hemorrhoidal veins above, but also with the veins of the perineum and scrotum. The blood is gathered into several large branches from a perineal plexus, and these branches usually unite before emptying into the internal pudic vein in Alcock's canal.

The middle hemorrhoidal veins are the most important in anastomosing the caval and portal venous systems. Through their connections they communicate both submucosally and perimuscularly with the inferior hemorrhoidal vein, drain the region of the rectum immediately above the internal sphincter and have free submucosal anastomosis with the superior hemorrhoidal vein. Their branches also anastomose freely with the prostatic or vaginal plexus and in some cases the middle hemorrhoidal vein becomes one of the principal veins to return blood from the urinary vesicle. From many ramifications the veins gather into larger branches on each side of the rectum, and, following the course of the middle hemorrhoidal artery upward, the final single trunks join the internal iliac veins.

The largest of the rectal veins are the superior hemorrhoidal. From as low in the rectum as the columns of Morgagni, the blood is collected by a large mucosal and submucosal plexus and returned upward in the submucosa. In this course the vessels unite to form larger twigs which eventually penetrate the thick muscularis of the rectum at an angle and then continue upward parallel to it. As higher branches from the mucosa penetrate the muscle they join the original veins which also receive branches from the perirectal tissues. Near the upper end of the rectum, large right and left veins are formed which accompany the corresponding branches of the superior hemorrhoidal artery. The veins receive small vessels from the region of the rectosigmoid and pelvic colon, and the vessel continues upward to the left of the median line, becoming the inferior mesenteric vein at the level of the left common iliac artery.

One of the early investigators of the veins of the rectum was Duret.[109] For practical purposes he divided the veins of the rectum into an external system, which drained downward into the perineum and internal pudic vein, and an internal system, which drained upward. The external system is anatomically the inferior hemorrhoidal vein with additions that it may receive from the middle hemorrhoidal vein. The internal system is composed of the middle, and principally, the superior hemorrhoidal veins. This division is still adhered to by surgeons, and the connection between the two and thus between the caval and portal systems has been in some dispute.

Duret found that he was able to inject material from the inferior mesenteric vein not only into the external hemorrhoidal system but into the saphenous, femoral and genital veins. Similarly, the superior hemorrhoidal vein could be injected from the internal iliac vein. Quénu,[110] in general, substantiated this study but believed that because of varying results there might be some form of valve between the two systems. Gay [111] maintained the independence of the two systems and has been upheld in his views by Cripps. Cripps thinks there is little connection between the veins of the two systems and that when there is, the flow is always toward the iliac veins. Tuttle has demonstrated the connection between the two systems and emphasized the difficulty of injecting the anastomosis of the two through the sphincter, which he compares to a watershed.

We would like to emphasize a fact here that seems to have been neglected. The middle hemorrhoidal vein is the largest medium of intercommunication between the portal and caval systems. Since the distribution and anastomosis of the middle hemorrhoidal artery are extremely variable, a similar variability may be expected in the middle hemorrhoidal vein, and the extent of anastomosis effected by the rectal vessels between the caval and portal systems will vary in each case.

SURGICAL CONSIDERATIONS

The mortality from operations on the colon has not only been reduced by modern study and technic, but operation is being attempted in more advanced cases, a fact which makes comparisons difficult. A large percentage of operations on the large bowel are performed because of malignant conditions, and the opinion as to the operability of a lesion varies with the surgeon. Therefore, a cautious operator may present

109. Duret: Recherches sur la pathogénie des hémorrhoïdes, Arch. gén. de méd. **144**:641 (Dec.) 1879.

110. Quénu, E.: Études sur les veines du rectum et de l'anus, Bull. Soc. anat. de Paris **6**:601 (July) 1892.

111. Gay, John: On Haemorrhoidal Disorder, London, J. & A. Churchill, 1882 p. 60.

low mortality percentages, as a result of having condemned as inoperable cases in which cure or palliation might have been secured by accepting greater risk. Thus the difficulty of knowing what a writer considers an operable lesion enters into the evaluation of statistics. Undoubtedly the last few decades have seen a widening in the field of operability and an increase in radical surgical procedures on the colon.

The primary purpose of the study of the blood supply of the large intestine was to apply it practically to surgery. Operations on this part of the intestinal tract are fraught with the danger of sepsis, even when most carefully performed, because of the type of bowel and nature of its contents, and the added peril of gangrene in the wall of the bowel from ischemia has undoubtedly been a contributing factor to the hospital death rate. With this thought in mind, an attempt has been made to apply the anatomic facts relating to the blood vessels to the operations usually performed on the large bowel. A description of the technic of the operation aside from its application to the blood supply has been purposely avoided. Some of these procedures have been described by previous writers, as few surgeons have written about the colon without giving some warning as to its circulation.

The colon and its blood vessels are roughly similar to a rubber-tired wheel with few, irregularly placed spokes. The spokes represent the named colic arteries, and the rim represents the marginal artery from which the colon is supplied by the terminal branches. It is important in handling the blood supply of the colon to keep in mind that the arterial pattern of each colon is original. The present study has established a few facts such as the continuity of the marginal vessel and the percentage of occurrence of the various named arteries, but the outstanding fact emphasized is the variability of the arterial pattern, making it essential to deal with each case as a variant. The fact that single colic arteries may be ligated experimentally or by mishap during an operation, and the supply to the bowel maintained by the marginal artery should not be an excuse for carelessness. These arteries should be ligated purposefully and only when occasion demands. The arteries of the colon are variable in size and position, and the two adjacent vessels should be investigated before one artery is occluded. The importance of this cannot be more emphatically proved than by reference to the celloidin cast shown in figure 5. Here ligation of the inferior mesenteric artery would inevitably result in ischemia and gangrene of more than half of the colon. The vessels to the portion of the bowel involved should be identified in all surgical procedures. Identification may be difficult in the presence of excessive fat or adhesions; however, a knowledge of the approximate situation of the vessels and palpation for their pulsations will usually establish their situation.

Mobility.—Mobility of the colon is a decided advantage in dealing with the blood supply. If the part of the bowel involved can be lifted

so that the mesocolon is vertical to the posterior wall, the blood vessels are easily identified even in the presence of moderate obesity. There is nearly always mobility in the transverse portion of the colon, and although we have found a mesocolon to be present in the ascending and

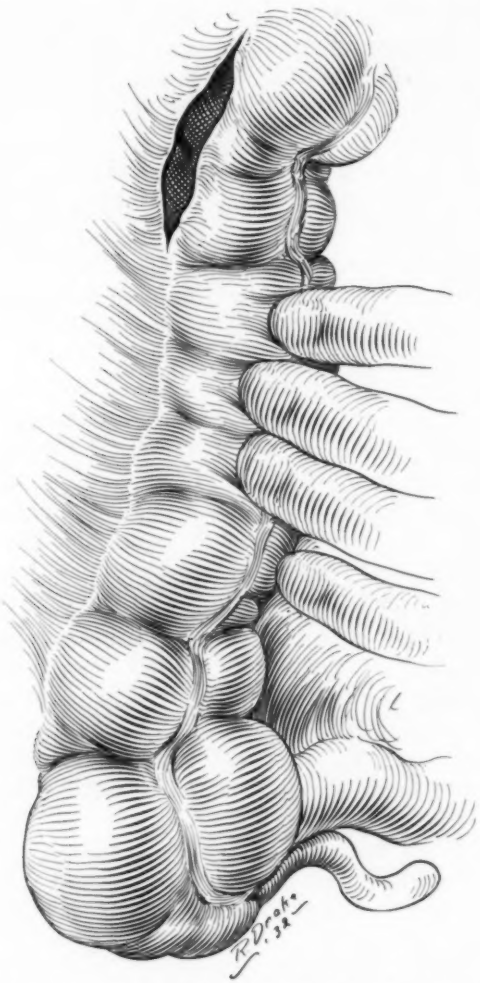

Fig. 17.—Incision along the line of the peritoneal reflection lateral to the colon to obtain mobility.

descending portions of the colon more frequently than Treves' classic figures indicate, it is usually too short to allow any appreciable upward manipulation. To obtain mobility, the peritoneum should be incised along the lateral side of the colon. There is usually slight thickening of the peritoneum at the line where the upward reflection from the

posterior wall takes place, and the resulting white streak may be incised throughout its entire length without danger of encountering vessels (fig. 17). The bowel may then be lifted mesially and upward and the centrally situated blood supply brought into prominent relief (fig. 18).

Insufficient mobilization of the colon, in the course of a procedure in which the bowel is to be fixed, may have several detrimental effects on the blood vessels. Undue pull on the colon will tend to stretch the

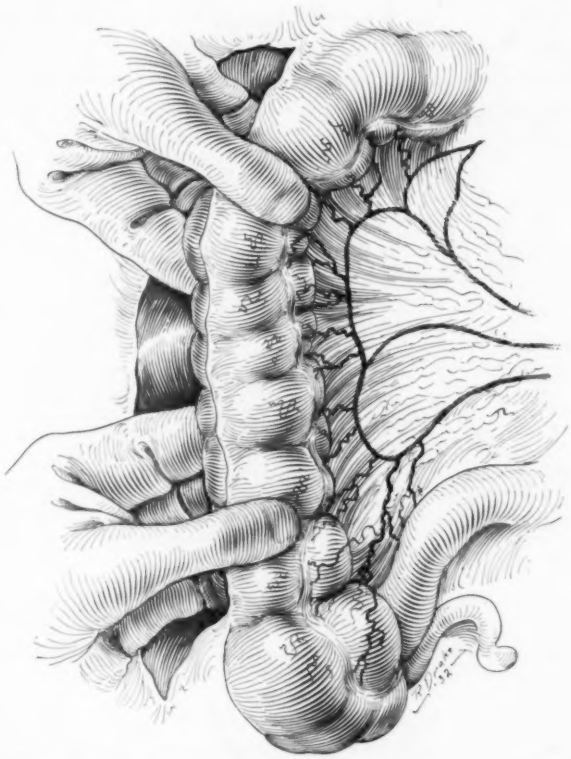

Fig. 18.—Colon elevated after incision of the peritoneum along line of its lateral reflection.

vessels to that part longitudinally and thereby decrease the diameter of their lumen. This is particularly true of the marginal and the terminal vessels. Another danger is that acute angulation of more distantly attached vessels may occur, especially at the points where the colon is permanently fixed by ligaments. The blood vessels of the colon lie beneath a loose peritoneal covering which allows considerable movement, and their attachments are only through their inosculations and terminal branches. For this reason, angulation of a vessel several centimeters distant may be caused by tension on the colon, thereby

reducing the anastomotic supply at a point where it is most necessary. This trouble is particularly likely to be encountered in operations in which the bowel is fixed to the wall of the abdomen, such as colostomy, and will be referred to again when these procedures are considered.

The Wall of the Colon.—In the study of the terminal vessels to the colon, we have stressed several important facts: (1) the comparatively scanty anastomosis between the small terminal arteries; (2) the greater vascular supply to the mesocolic two thirds of the bowel, and (3) the subserosal position of the long arteries before they pass beneath the two amesocolic taenia to supply the relatively avascular third portion of the colon. These anatomic peculiarities give us several guides in surgical procedures on the wall of the bowel. The slight anastomosis of the

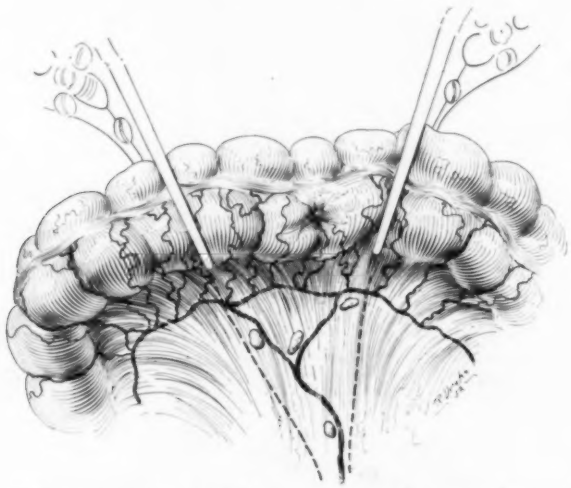

Fig. 19.—Colon cut across at angle to preserve the mesocolic, vascular portion.

arteries demands greater care in handling the large intestine than the small. When the bowel is to be cut across, as for end-to-end anastomosis, a greater part of the vascular mesocolic portion of the colon should be retained than of the amesocolic third. This is accomplished by cutting the bowel at an angle (fig. 19). If the colon is cut perpendicular to its axis, the incision may just include one of the long terminal branches to the amesocolic portion, thus destroying for perhaps 2.5 cm. the only supply to a naturally impoverished portion of the bowel. Pauchet,[112] without considering the course of the vessels, advocated cutting the colon at an angle of 45 degrees. So great an angle might make it difficult to obtain sufficient mobilization to avoid

112. Pauchet, Victor: Practical Surgery Illustrated, London, Ernest Benn, Ltd., 1925.

pull on the amesocolic part of the anastomosis in cases in which the colon was large and would result in a sharp angle in the lumen. A more rational rule would be to cut the bowel at less acute angles, so that the two ends will most closely coincide in diameter. Cutting the colon at an angle has the added advantage of producing a larger opening at the anastomosis.

When a longitudinal incision in the colon is necessary, it should be placed in the center of the amesocolic third of the bowel (fig. 20). The closer a longitudinal incision is made to the mesocolic taenia, the greater will be the area of colon between the incision and the outer point on the circumference of the bowel to be furnished by the feeble anastomosis of the encircling arteries of the opposite side and the adjacent terminal vessels. The direct supply to the area will have been sacrificed, and the danger of gangrene will be commensurate with

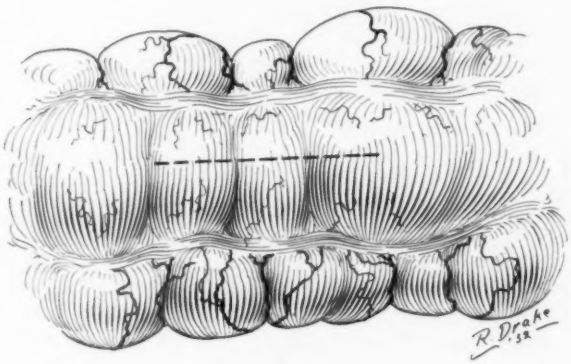

Fig. 20.—The dotted line indicates the site of ligating the marginal artery and resecting the main artery when necessary.

the length of the incision. Fortunately for patients and surgeons, the amesocolic section of the colon is usually the most accessible and the least encumbered with fat, and therefore is the place usually selected for ileocolostomy and insertion of enterostomy tubes. If the anatomy of the terminal vessels to the colon is kept in mind, the surgeon will make only longitudinal incisions in the colon parallel with, and exactly between, the amesocolic longitudinal bands.

The subserosal course of the long terminal arteries exposes them to considerable danger when an effort is made to clear fat away from the colon. These arteries furnish branches to the epiploic appendages before passing beneath the longitudinal muscles to the amesocolic section of the wall. In elevating and clamping fat tabs, it is easy to include the long artery, especially if the colon is contracted, and there is increased redundancy of the arteries. Since these arteries are the sole supply to the outer third of the colon, their value cannot be over-

estimated. As an experiment, the long arteries have been intentionally included when cutting off the epiploic appendages of colostomy loops which are later to be trimmed off and remain as permanent colonic stomas. Usually, although not invariably, there results an area of necrosis in the wall of the bowel near the median line between the taenia. In one case in which the long arteries were ligated on opposite sides of the colon at the same point, necrosis of the wall between the longitudinal bands occurred for about 2.5 cm., the opening, which appeared on the fifth day, being circular. Although there may have been slight impairment of the circulation to the colostomy loop, the resulting necrosis can be regarded only as evidence of the avascularity of this part of the colon and emphasizes the advantage of leaving the

Fig. 21.—The correct (left) and incorrect (right) method of clamping epiploic appendages.

long terminal vessels intact. To avoid injury to the blood supply, the epiploic appendages should not be pulled outward too vigorously, and the clamp should be placed on the neck of the tab, parallel to a tangent at the longitudinal muscle band (fig. 21). The mesocolic fat should be removed by blunt dissection.

The Marginal Artery.—This artery has been found to be a continuous vessel present in all colons. In a small number of ascending colons (5 per cent), it is replaced by profuse single branches. The distance of the artery from the wall of the bowel varies from a half to several centimeters, and the presence of secondary loops is uncertain. In position and function, the marginal artery is comparable to the water main in a city street. Whenever possible, the artery should be left intact. However, its presence assures the colon of a distal as well

as proximal blood supply, and whenever the occasion demands, the surgeon should have no hesitancy in resecting the marginal artery of the part of the intestine being removed. In fact, it may be desirable in cases of malignant conditions when it is recalled that the second set of lymph nodes, the paracolic nodes, follows its arcades down to the main arteries. When the marginal artery is resected, care should be taken that the remaining artery extends beyond the cut edge of the colon which it supplies (fig. 19). The principle of the wedge or fan-shaped resection applies to resection of the mesocolon with its blood vessels quite as much as to that of the mesentery of the small bowel. Should the wedge of mesocolon include one of the main colic arteries, the artery itself should be made the apex of the resected wedge and ligated as close to its source as is compatible with proper peritonealization of the posterior wall. In this way the resection would include the third set of lymph nodes, the intermediate nodes, which follows the course of the colic arteries.

Colostomy.—The oldest operation on the colon is colostomy.[113] Regardless of the type or position of the colostomy, there are a few fundamental rules which should be remembered with regard to the blood vessels. The colon must be sufficiently mobilized to allow the bowel to extend above the skin of the abdomen without undue pull upward on the peritoneal attachments. This may be accomplished by incising along the lateral peritoneal reflection as described. With the colon freed to allow exteriorization of a small loop without undue pull on the underlying arteries, the immediate vessels must be considered. The marginal artery will be found running more or less parallel with the wall of the colon at a distance varying from a half to several centimeters. This vessel should always be left intact when colostomy is performed as it is the immediate source of supply to the colon and the important anastomosis between the arteries of the colon. In the types of colostomy in which it is desirable to make an opening in the mesocolon, either to draw components of the abdominal wall together below the loop or simply to fix the loop in position on a tube or rod, the opening should be made between the colon and the marginal artery (fig. 22). In order to obtain an opening of sufficient size, it may be necessary to ligate several of the terminal vessels, but this is preferable to ligating the marginal artery or making the opening beneath it. Ligation of the vessel may rob the colon proximal to the colostomy of a valuable anastomotic blood supply, whereas an opening below the artery adds to the first danger a second from the embarrassing amount of bleeding produced by the relatively simple process of cutting across the colostomy opening.

113. Reference Handbook of the Medical Sciences, New York, William Wood & Co., 1900, vol. 1, p. 532; 1901, vol. 2, p. 105.

Some surgeons customarily sew the peritoneum to the elevated colon after performing colostomy. Although we believe that sewing into the colon should be avoided whenever possible, we wish to emphasize here only a point regarding the blood supply. In the mesocolic portions of the colon, the vessels lie loosely beneath the serosa and are often covered with fat. In sewing the peritoneum to the wall of the colon, it is easy to injure or ligate several of the long terminal branches.

Mikulicz Operation.—This operation, which is occasionally performed for malignant disease of the colon, is exteriorization of the loop

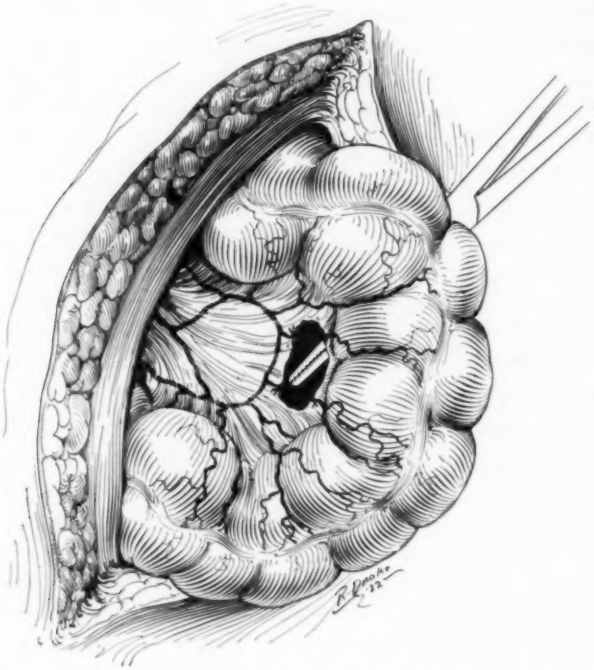

Fig. 22.—Opening between the colon and marginal artery in performing colostomy.

containing the growth, with removal as a second stage of the procedure. It entails several factors into which the blood supply enters. The first consideration is proper mobilization of the part. The procedure is generally reserved for the encircling scirrhous types of malignant growths that make intra-abdominal manipulation hazardous. If this type of lesion is pulled upward under any tension, some circulatory disturbance may result. Since the veins are more easily collapsed than the arteries, passive congestion of the already highly infected mass occurs. The resulting compensatory dilatation and hyperactivity of the lymph channels will carry the infection, if not the malignant growth

itself, downward into the abdominal cavity. To avoid vascular embarrassments, the first consideration in the Mikulicz operation must be sufficient mobilization of the growth and colon to be resected.

Resection.—Resections of parts or all of the colon must be adjusted to the nature of the lesion. There is no advantage in removing the marginal vessel and the main arteries in cases of benign lesions such as polyposis or ulcerative colitis. The handling of the wall of the colon and the marginal artery in resection has been considered, and we wish here merely to advocate primary ligation of the main arteries to the part to be removed. In any case in which an appreciable portion of the colon is to be removed, the operation can be greatly simplified and shortened by ligating the vessels to the part in their central position before an attempt to remove the bowel is made. This necessitates careful identification of vessels and may not be feasible if the patient is obese. For example, in the removal of the right portion of the colon after ileocolostomy has been performed, if the ileocolic, the right colic and the marginal arteries just distal to the anastomosis are ligated first, resection can be made without further clamping and only a negligible amount of blood will be encountered in the distal vessels (fig. 23).

Resection of the splenic flexure frequently offers great difficulty from the technical standpoint. It has been shown that the marginal artery is present in this region, at least before operation, and that there is no lack of blood to the part. However, the splenic flexure lies high, and is deeply placed within the abdomen in the form of a long, inverted U. The blood vessels to the region, through the marginal artery, are almost parallel and close together. If resection of this part is attempted from the median aspect, the marginal arteries are in grave danger of being injured at points proximal to the site of resection. The attack must be lateral to the colon, freeing the splenic flexure along the white line of the peritoneal reflection, severing any connection between the omentum and the spleen and any peritoneal attachments of the colon to the posterior wall. The entire splenic flexure may then be brought mesially and upward with the arteries uninjured, and the resection may proceed as conditions indicate. It would be well to recall that the left part of the transverse colon may have lymphatic drainage upward to the spleen through the thickened left edge of the omentum. For this reason it is advisable to remove this part of the omentum.

Sigmoid.—The sigmoid offers the most favorable site for operations on the large bowel from the standpoint of dealing with blood vessels. The mesosigmoid allows easy exposure of the affected part; the arterial supply is adequate and flexible, due to the secondary loops usually present below the marginal artery, and in addition the sigmoid is low in the abdomen where infection is less dangerous than near the diaphragm. The same rules that apply to handling the blood supply of the colon are applicable in operations on the sigmoid.

Rectosigmoid.—In the region of the lower portion of the sigmoid near the rectum, the form of the blood supply changes. The region has been generally referred to as the rectosigmoid, and from the standpoint of the blood supply, is characterized by lack of the marginal artery, doubtful anastomosis with the arteries of the sigmoid through the small last sigmoid artery, more longitudinal direction along the bowel of the small arteries to the wall and loss of the mesosigmoid in the base of which lies the large superior hemorrhoidal artery. Consider-

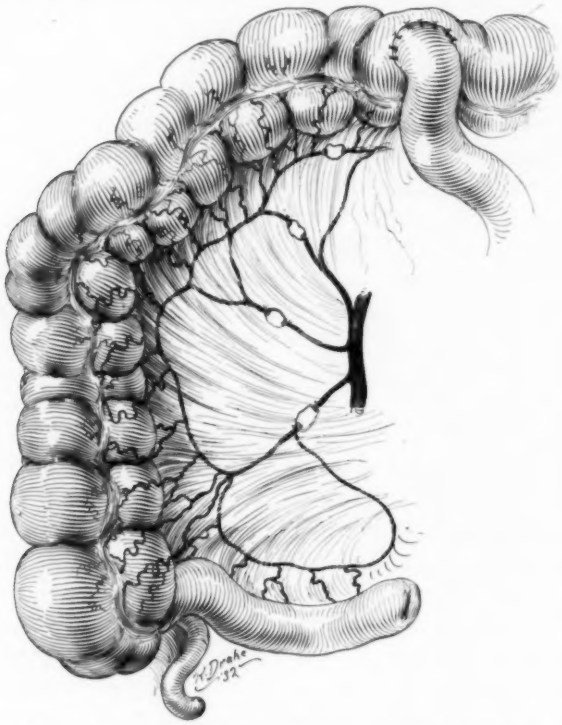

Fig. 23.—Primary ligation of the vessels in removal of the right portion of the colon.

able interest was centered about the part several years ago, when it was customary to pull the sigmoid down and make a posterior artificial anus after resection of the rectum. It was the custom to sever the superior hemorrhoidal artery through an intra-abdominal incision in order to allow sufficient mobility of the sigmoid to bring it down. Sudeck, in studying the vessels of this region, described what was called a critical point for this ligation, just above the last sigmoid artery, which was supposed, through its anastomosing with the marginal artery of the sigmoid, to replace the blood supply to the rectum. If the superior

hemorroidal artery were severed below this point, necrosis of the rectum would result. Later, Drummond [88] studied the region and found that there was no anastomosing artery between the marginal artery and the superior hemorrhoidal artery in 10 per cent of the cases, and that the artery was so small that it was negligible in 40 per cent. The critical point was then moved upward and located just below the first sigmoid artery. However, the sigmoid arteries are extremely variable in their origin and number. They may all rise from the left colic artery or from one large branch of the inferior mesenteric artery. Fortunately, operations making the artificial anus posteriorly have been largely discarded, but the question of blood supply to the rectum is still present in two-stage abdominoperineal resections. Because of variations in the arterial supply in this region, there is but one safe rule to follow: If the superior hemorrhoidal artery is severed, the bowel below that point should be removed at once.

Rectum.—In the rectum, the character of the arterial supply is altered even more noticeably than in the rectosigmoid. The branches of the superior hemorrhoidal artery course downward along the rectum and pass through the thick muscular walls to the submucosa. In the lower part of the rectum, the variable middle hemorrhoidal artery enters to form an anastomosis with the superior hemorrhoidal artery above, and below with the inferior hemorrhoidal artery which supplies the anal canal. Because of the longitudinal direction of the vessels, it is possible to perform posterior resection almost bloodlessly after the lower vessels have been ligated. The superior hemorrhoidal artery is isolated late in the operation on the posterior surface of the rectum or rectosigmoid. There is no danger of ischemia following ligation of this artery, as the bowel below the point is entirely removed. This is likewise true for the less radical local excisions of growths low in the rectum.

The marked variations of the middle hemorrhoidal artery and its frequent rôle as a vesical artery perhaps account for some of the complications encountered in posterior resections of the rectum. The dysuria and retention so marked in some cases following ligation of the hemorrhoidal arteries, may result from having a considerable portion of the supply of blood to the bladder cut off, with consequent increased neurogenic disturbance. Similarly, an occasional vesical fistula following a posterior resection of the rectum may be caused by the ligation of a middle hemorrhoidal artery that was furnishing a large part of the blood to the posterior aspect of the bladder.

CONCLUSION

A thorough study of the blood supply of the large intestine shows conclusively the variability of the arterial patterns, and for this reason the suggestions for surgical procedures are made as general as possible.

EXPERIMENTAL PLEURAL ADHESIONS

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A variety of surgical procedures for abscess of the lung is in practice at the present time, ranging from simple drainage, unroofing and ventilation to pneumonectomy. The most dangerous complication of these operative procedures is entry of the free pleura with resultant fatal putrid empyema. A lung with a putrid focus and a nonadherent, or inadequately adherent, pleura at the site of the focus, therefore, contraindicates operation until adequate adhesions have been formed to prevent pleural invasion. We accept the idea that the pleura partakes in the process of infections of the lung, such as abscess and, sometimes, bronchiectasis. In abscess of the lung the infection is lodged in the smaller bronchi in the early stage of the disease. The lung then undergoes a process of putrid liquefaction, and a more or less extensive surrounding pneumonitis ensues. The adjacent pleura is involved with a resulting pleuritis. As the process extends, the area of pneumonitis enlarges, the pleuritis becomes more extensive and adhesions are formed between the two layers of the pleura. Since the putrid focus is localized in its extent, the pleural involvement, or the pleural adhesions, will be more or less localized over the area of the putrid focus in the lung. Provided exact localization of the abscess has been carefully determined by roentgenographic examination or studies with iodized poppy seed oil 40 per cent, it remains a simple matter for the surgeon to resect a rib or ribs, encounter the pleural adhesions and drain the abscess cavity through them. Nevertheless, even with an abscess exactly localized, the area of pleural adhesions may be too limited or inadequate for a safe procedure. At the edge of the zone of pneumonitis, the pleural adhesions may be weblike in structure. This is especially true in acute abscess of the lung. Any degree of exploration beyond the limited zone of firm adhesions may result in a general pleural infection.

This problem of the surgical treatment of suppurative pulmonary foci is entirely dependent, therefore, on the production of an effective pleural barricade to an infected focus. That this fact is generally recog-

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nized is shown by the practice in some clinics of attempting to produce adhesions by suture and by packing with gauze, in order to wall off the putrid focus in the lung prior to operation. The importance of pleural adhesions in operations on abscess of the lung also explains the many attempts at experimental production of pleural adhesions by the intrapleural and the extrapleural routes. Since pleural adhesions could be produced by any one of these methods, it occurred to us (Drs. Hirshfeld and Cohen), while working on the problem of abscess of the lung at Mount Sinai Hospital, to review the available methods from the point of view of efficacy of their production, the simplicity with which they could be formed and the factor or factors underlying their formation.

Intrapleural injections of solutions, such as 50 per cent dextrose, glycerin, gum arabic solutions in varying concentrations, turpentine and corrosive chemicals, were tried and either gave a violent pulmonary reaction in animals or did not inaugurate any pleural reaction whatsoever. It is judged that the intrapleural injection of these substances to produce pleural adhesions is dangerous for clinical trial.

Of the extrapleural methods the application of chemicals was first tried. When chemicals are applied to the endothoracic fascia, either a local abscess or a simple inflammatory process may ensue without giving rise to pleural adhesions. In some cases they may give rise not only to a pleuritis which results in adhesions, but in addition to a rather violent pneumonitis. The procedure associated with the least danger, and the greatest efficacy was found to be extrapleural compression. This was accomplished by packing tightly against the endothoracic fascia beneath a rib. Both gauze and sea sponges were used to produce extrapleural compression. In each case adhesions were produced, showing that the common factor responsible for the production of adhesions in the pleura was the effect of pressure, irrespective of the substance or substances used.

EXPERIMENTS

A limited number of experiments were done to note the effect of application of chemicals to the parietal pleura. A number were also done to note the effect of extrapleural compression by means of gauze or sponges. Microscopic sections were made of specimens showing pleural adhesions. Only typical experiments will be cited, and a few illustrative microscopic sections will be fully described.

Dog 11072.—On Oct. 22, 1931, with the animal under ether anesthesia, two ribs were resected on the left side for about 3 inches (7.6 cm.). Intercostal muscles were removed. Gauze soaked in turpentine in olive oil (1:2) was applied to the parietal pleura. The gauze was left in place for about fifteen minutes and then removed. The dog was killed on October 29. Postmortem examination disclosed no pleural adhesions.

Dog 11114.—On Nov. 12, 1931, with the dog under ether anesthesia, the fifth and sixth ribs on the right side were removed for a distance of about 3 inches. Gauze soaked in oil of eucalyptus was applied to the parietal pleura and was then removed. The same procedure followed on the left side. The dog was killed on November 19. Postmortem examination disclosed that both right and left pleural surfaces were intact and free from adhesions.

Dog 11073.—On Oct. 22, 1931, with the dog under ether anesthesia, two ribs were resected subperiosteally on the left side for a distance of about 3 inches. Two layers of gauze soaked in turpentine in oil (1:2) were packed into the wound extrapleurally. The wound was closed in layers. The dog was killed on October 26. Postmortem examination disclosed a large subcutaneous abscess at the site of application of gauze with the oil. In addition there was a diffuse bronchopneumonia in the underlying lung. The pleurae were free of adhesions.

Dog 11089.—On Oct. 29, 1931, with the dog under ether anesthesia, two ribs were resected subperiosteally on the right side. The parietal pleura was exposed and was then soaked with eucalyptol over an area measuring about 6 inches (15.2 cm.). The wound was closed in layers. The dog was killed on November 5. Postmortem examination disclosed adherent pleura over the area painted with eucalyptol. The right lung was adherent to the pleural surface over an area about 2 by 5 cm. The parietal pleura adjacent to the adhesions was reddened and thickened.

Microscopic Examination.—A section through the thoracic wall and the adherent lung showed that the lung was fixed to the wall of the chest by a delicate granulation tissue well supplied with fibroblasts, capillaries and slender collagen fibers. The adjacent lung showed an interstitial infiltration with phagocytic cells and a dilatation of the interstitial capillaries which extended throughout the entire adherent piece. There did not seem to be any alveolar exudate or any exudate in the bronchi. The parietal and visceral pleurae on either side of the adhesions were covered with a thick fibrinous exudate mixed with many red blood cells and a moderate number of polymorphonuclear leukocytes and mononuclear cells. Beneath this exudate was newly formed granulation tissue. In the thoracic wall all of the tissues were edematous and the inflammatory reaction had separated many of the muscle fibers. In some areas there had been extravasations of red blood cells and a proliferation of fibroblasts. In some areas, also, there were huge numbers of phagocytic cells, some of them of giant proportions. Many of these seemed to contain foreign material which possibly bore some relation to the eucalyptol, although no definite oily droplets were found.

One got the impression that there had been a tremendous inflammatory response to the eucalyptol which had resulted in a fibrinous exudate on the pleural surfaces. This, however, had not been destructive enough to prevent the growth of adhesions between the visceral and parietal pleurae.

Dog 11159.—On Dec. 3, 1931, with the animal under ether anesthesia, two ribs were exposed on the left lateral wall of the chest. Parietal pleura with the periosteum was stripped from both ribs for a distance of 3 inches. Intercostal muscles between the two ribs were excised. A packing of gauze soaked in eucalyptol was placed beneath the ribs extrapleurally so as to get extrapleural compression. The dog was killed on December 10. Postmortem examination disclosed extensive adhesions of pleura over the area where the gauze was placed. Superficial muscles about the area of operation were edematous and red. Adhesions between the pleurae covered an area of about 6 inches and were very firm.

As is seen from the foregoing experiments, the application of chemicals, oil of eucalytus or oil of turpentine to the parietal pleura either fails to produce adhesions or may induce an abscess in the superficial tissues with bronchopneumonia in the underlying lung. In only one experiment in which a great deal of eucalyptol was used was a severe pleuritis with adhesions produced. When chemicals are applied with extrapleural compression, a severe inflammation of the surrounding tissue ensues with the production of adhesions.

Dog 10775.—On Feb. 5, 1931, with the dog under ether anesthesia, a small section of the second rib anteriorally on the right side was removed. The pleura was entered and closed by mattress sutures of the lung of the soft parts. The pleura was stripped down over an area below the rent, and three large pieces of sterile sea sponge were inserted to produce extrapleural compression. The wound was sutured in layers.

The dog died on March 11. Postmortem examination on March 12 disclosed a tension pneumothorax below the wound. The lung was firmly adherent to the wall of the chest where it had been sutured. Sponges showed early organization, and the pleural surfaces were adherent deep to the area of compression.

Dog 10802.—On Oct. 3, 1931, with the dog under ether anesthesia, gauze packing was placed beneath the fourth and fifth ribs after the periosteum was stripped away. Pressure was applied to the underlying pleura and lung by tight packing of gauze. The dog was killed on December 10. Postmortem examination showed the entire lung adherent to the lateral thoracic wall. On the external surface was the opening of a cavity from which most of the gauze packing had been removed. In its depths two ribs were exposed, and both were denuded of periosteum. The deep surface of this cavity was formed apparently by the fusion of parietal and visceral pleurae. They were so fused that they could not be separated. The lung deep to the area of direct pressure represented by the cavity seemed compressed and paler than the rest of the lung, although it was still air-containing. The main bronchial divisions were unaffected insofar as their caliber was concerned.

Outside of the area of direct pressure, organized adhesions joined the parietal and visceral pleurae for a variable distance. Anteroposteriorly, the adhesions covered the entire external surface of the lung. From above downward about half of the external surface of the lung was fixed to the thoracic wall. Adhesions had fixed the interlobar pleural surfaces together.

Microscopic Examination.—A large section had been taken through the lung, a portion of the cavity with the adhesions on either side of it and the lateral thoracic wall. Where the pleurae were adherent to one another, the adhesion was formed by a thick layer of fibrin into which fibroblasts and capillaries had grown from both surfaces but at the place where the section was made had not completely bridged the gap. The cavity itself and all the visceral and parietal pleurae were covered with a fibrinous exudate with many inflammatory cells, into which fibroblasts and capillaries had grown. Some of the interlobar pleurae had complete cross fibrous union. On the lung side of the cavity the visceral and parietal pleurae had been fused and were united by complete fibrous union.

The lung showed many patches where the alveoli were filled either with an acidophilic, finely granular material or with red blood cells. There was little exudate of cells and these were found chiefly in the septums. The bronchi had some exudate in them, chiefly of phagocytic cells. The wall of the chest showed

some fibroblastic proliferation between some of the muscle bundles, some degeneration of individual muscle fibers and a subperiosteal formation of bone on the pleural side of two of the ribs.

Dog 11189.—On Dec. 17, 1931, with the animal under ether anesthesia, the sixth rib was exposed on the left thoracic wall. The periosteum was stripped for a distance of about 3 inches. Two inches (5 cm.) of the rib was resected. Packings of gauze were placed in a circular fashion under both open ends of rib and under adjacent upper and lower ribs.

The dog was killed on December 22. Postmortem examination showed the left pleura adherent in a circular fashion at the points where the gauze was applied.

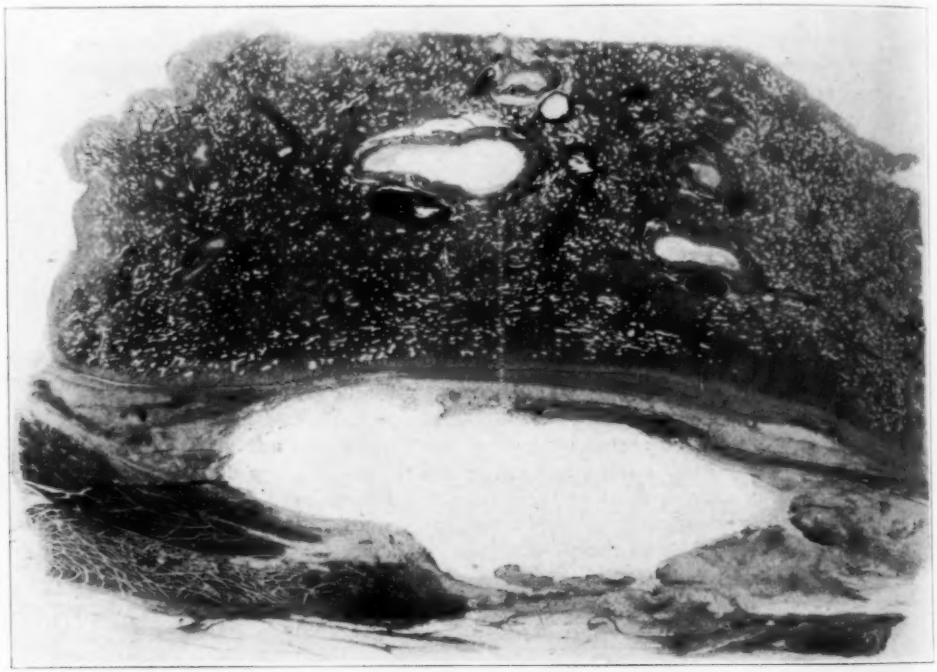

Fig. 1 (dog 11189).—Fibrous adhesions join the parietal and visceral pleurae beneath the cavity from which the gauze had been removed. The underlying lung was partly air-containing.

After making longitudinal sections paralleling the ribs, a large cavity was found tightly packed with gauze. From above downward this measured 6 cm. The cavity was bounded mesially by what seemed to be fused lung and parietal pleura, while laterally was the wall of the chest. Here the ends of the denuded and partially resected sixth rib projected into the cavity separated by a space 1.3 cm. wide. The whole cavity was lined with a dirty yellowish membrane to which the gauze was not adherent. The adhesions between the lung and the pleura about this cavity varied from 5 to 10 mm. in width. The underlying lung seemed compressed and hemorrhagic, but was air-containing. The entire visceral and parietal pleural surfaces seemed dull and thickened.

Microscopic Examination.—A section had been made through a portion of the cavity where it was about 2.5 cm. wide. The section had been made parallel with the rib and included the lung and wall of the chest. The cavity which contained the gauze was lined with granulation tissue and in places had some fibrinous exudate on its surface. The mesial portion of the cavity showed that the parietal pleura together with an intercostal nerve and vein had been forced inward by the pressure of the gauze (fig. 1). The parietal pleura was united firmly to the visceral pleura by a membrane composed of fibrin, capillaries, fibroblasts and collagen fibers which varied from 0.25 to 1 mm. in width (figs. 2 and 3). As one passed away from the zone of greatest pressure the visceral and parietal pleurae were more widely

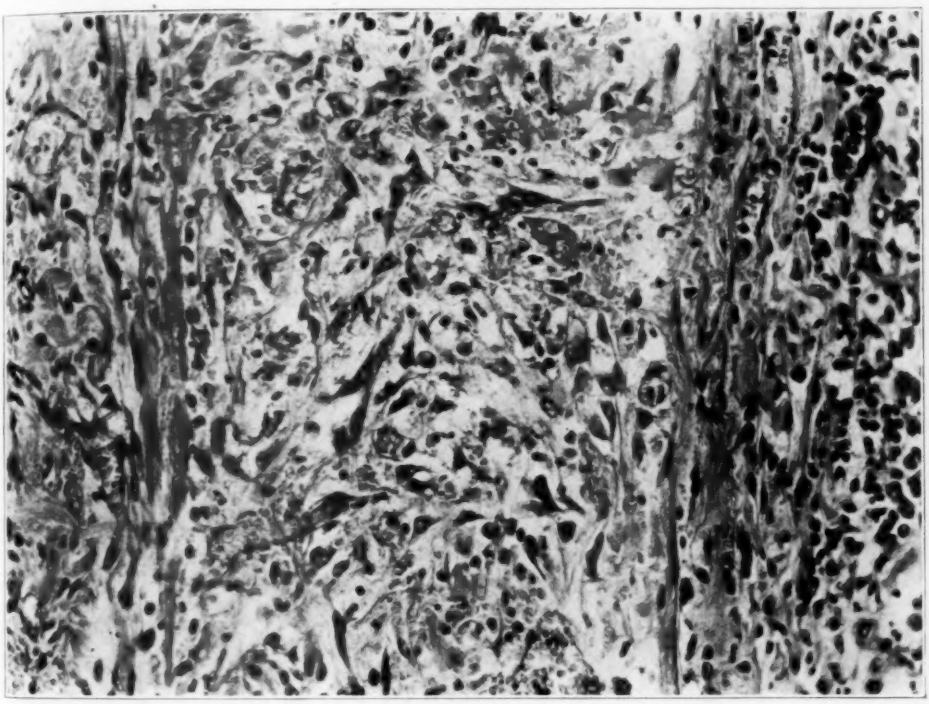

Fig. 2 (dog 11189).—A section stained with Masson's trichome stain. The firm union between the parietal pleura at the left and the visceral pleura at the right is shown. The space between the pleurae is filled with fibroblasts, blood vessels, collagen fibers and remnants of fibrin.

separated and the strong fibrinous adhesions had not been completely organized. The compressed lung showed that many of the alveoli were solidly filled with red blood cells, phagocytic cells containing blood pigment and alveolar cells (fig. 4). In some of the bronchi there were mucin and some cellular exudate. A section of the parietal pleura at a long distance from the region of compression showed that there had been a subpleural proliferation of fibroblasts and capillaries so that even here the pleura was much thickened.

From the foregoing and other unquoted experiments on dogs, it seemed evident to us that with extrapleural compression, either by

gauze or by sea sponges, firm pleural adhesions could regularly be formed. The adhesions joined the pleurae not only in the compressed area but for a variable extent outside of it. We believe that the area of pleural adhesions may be directly related to the degree of compression. By varying the degree of compression the adhesions may be either greater or less in area. We wish to emphasize the time interval at which the fibrous adhesions are formed. In the case of extrapleural compression with gauze, we found them well developed after from five to seven days.

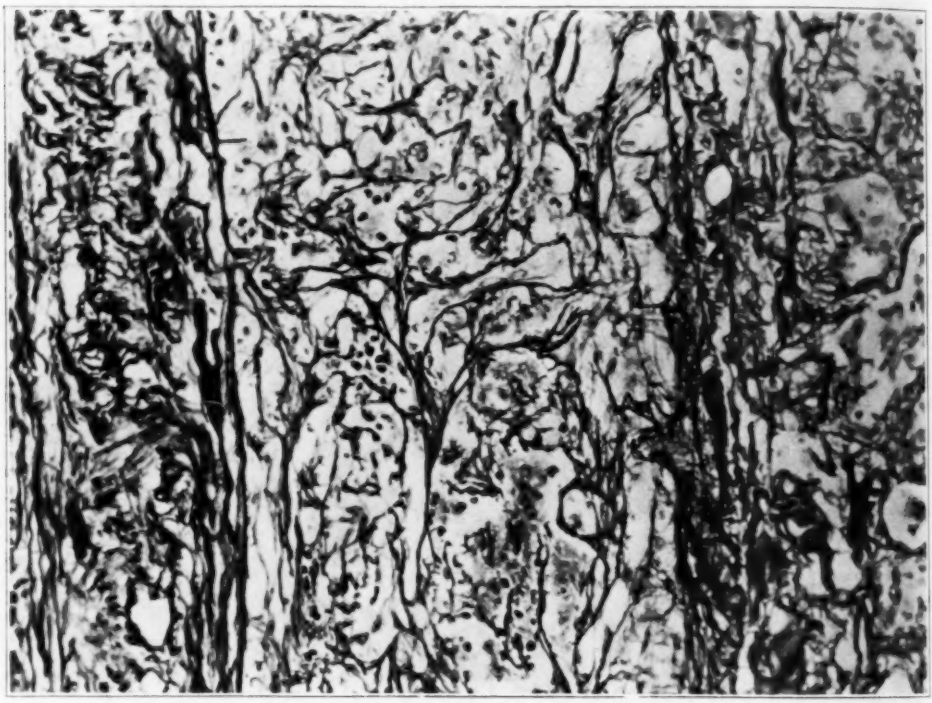

Fig. 3 (dog 11189).—A section stained with Laidlaw's stain. The area is similar to that seen in figure 2, and shows the density and number of the new reticulin (collagen) fibers. The fibroblasts are unstained.

COMMENT

Although pleural adhesions were produced by the extrapleural application of eucalyptol, we believe there are two objections to its use: (1) It is unreliable, and (2) it produces an excessive inflammatory reaction. In our experiments the application of pressure over the pleural surfaces with gauze or sea sponges always resulted in the formation of organized pleural adhesions, usually in from five to seven days without marked associated inflammatory response on the part of the lung. The

primary response in the pleura was a fibrinous exudate which rapidly became organized by fibroblastic tissue. The inflammatory reaction in the lung was minimal, and the bronchial exudate was composed of phagocytic cells.

Of the substances used to produce extrapleural compression gauze offered the best assurance of firm pleural adhesions in the shortest

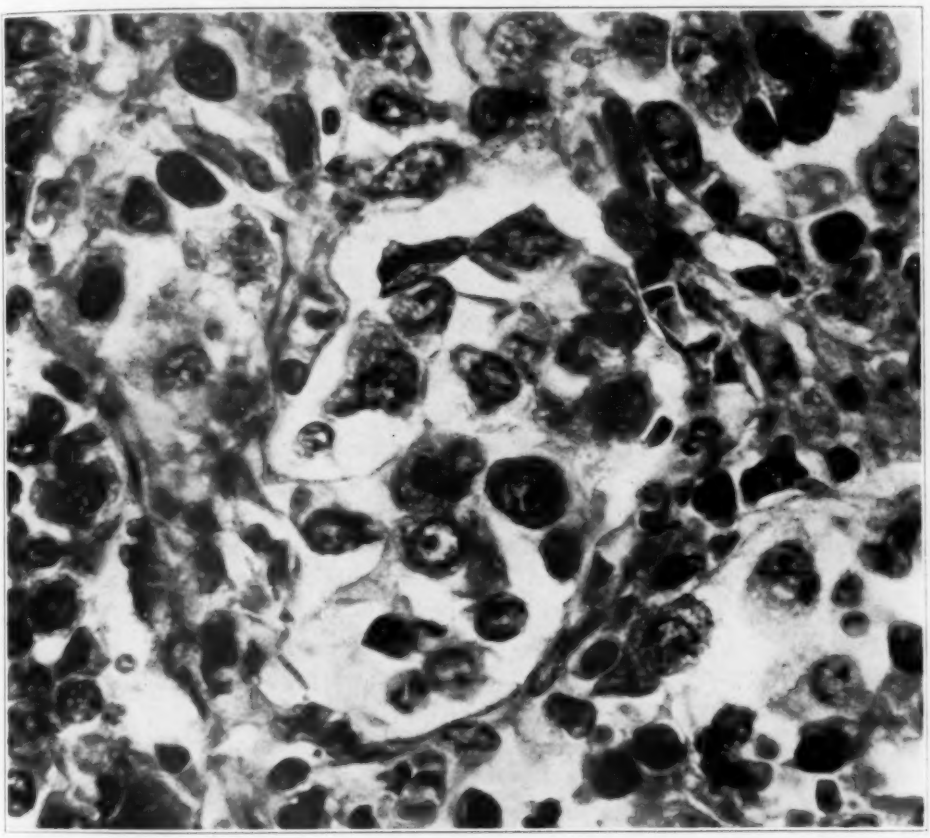

Fig. 4 (dog 11189).—A section showing the alveoli of the lung near the pleural surface filled with alveolar and mononuclear phagocytic cells.

period of time. The degree of compression with gauze could be controlled by varying the number of strips applied under the ribs.

In this paper it has been assumed that if the pleurae are sufficiently compressed to damage their lining cells, they will be joined by organized fibrous adhesions. In this process we believe that the following factors play a rôle: (1) the presence of a foreign body, such as gauze; (2) partial atelectasis of the lung tissue immediately underlying the area of compression; (3) reflex immobility of the lung and pleura as the

result of the injury, and (4) stretching of the parietal pleura away from the support of the endothoracic fascia and ribs.

According to Gay, local immunity may be the result of an increased cellular defense mechanism as it is expressed by the local cellular reaction. The most important element in the localized tissue response is the clasmatocyte. Gay and his associates [1] injected into the pleural cavity of rabbits suspensions of aleuronat or a gum arabic broth solution. After a certain lapse of time, usually from forty-eight to seventy-two hours, the polymorphonuclear pleural exudate was replaced by one containing mononuclear cells. The newly formed mononuclear exudate had the property of phagocyting highly virulent streptococci when these were injected into the pleural cavity, and the animal survived.

Since the tissue response to the application of pressure to the pleural surface is in the main composed of clasmatocytes, an additional cellular defense mechanism may thereby be afforded the pleurae against invasion of highly virulent organisms. This additional protection may be incidentally brought forth in the course of mechanical protection the pleural adhesions afford as a result of pressure.

SUMMARY

1. The extrapleural application of chemicals produces destruction of tissue with a great deal of inflammation.

2. The application of mechanical pressure by means of gauze packing or sea sponges against the external surface of a dog's parietal pleura results in the formation of fibrinous adhesions between compressed opposing pleural surfaces which, after five to seven days, are organized by the ingrowth of fibroblasts, collagen fibers and capillaries.

3. The pleurae at some distance from the area of the application of pressure appear thickened by fibroblastic and capillary proliferation.

4. The fibrinous pleural exudate apparently follows damage to the pleural cells from the extrapleural pressure.

5. The maintenance and organization of the fibrinous adhesions are aided by the partial atelectasis and immobility of the lung and by the stretching of the parietal pleura away from the support of the ribs.

6. The local tissue response consists, in part, of phagocytic cells.

7. This clasmatocyte response may have some bearing on local tissue resistance and immunity.

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1. Gay, F. P.; Clark, A. R., and Linton, R. W.: Histologic Basis for Local Resistance and Immunity to Streptococci, Arch. Path. **1**:857 (June) 1926.

ACTION OF NORMAL SKIN ON BACTERIA

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AND
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The object of this study has been to evaluate by a new method the action of normal human skin on bacteria. The method used by previous workers has consisted essentially of applying bacteria to skin and subsequently culturing the skin at different times. Although different workers have made similar observations with this method, unfortunately there has been marked disagreement in regard to the interpretation of the results. On the one hand, Arnold, Gustafson and their associates in a series of papers [1] believed that they showed that the disappearance of bacteria from the skin is due to its self-sterilizing action. Norton and Novy,[2] on the other hand, although confirming the rapid disappearance of organisms from the skin, believe that this is not due to any inherent germicidal action of the skin, but rather to drying. The subject is one of importance to surgeons and others, and it has seemed of value to pursue it further. In this study, instead of applying bacteria to skin, we have applied skin to agar plate cultures of bacteria.

METHOD

The skins of 6 apparently normal subjects, 3 men and 3 women, were tested.[3] Twelve strains of bacteria, of 7 genera, were used. Tests with not more than 2 fingers a day for each person were made with any organism, so that finally tests had been made on over fifty days. This seemed sufficient to cover daily variations. Tests were made as follows: Tubes of melted, cooled agar were inoculated with a 3 mm. loopful of 1:10 broth dilutions of twenty-four hour broth cultures. Plates were poured immediately after inoculation and allowed to harden

From the James Buchanan Brady Urological Institute, the Johns Hopkins Hospital.

1. Arnold, L.; Gustafson, C. J.; Hull, T. G.; Montgomery, B. E., and Singer, C.: Am. J. Hyg. **11**:345, 1930. Singer, C., and Arnold, L.: Proc. Soc. Exper. Biol. & Med. **27**:364, 1930. Karns, R., and Arnold, L.: ibid. **28**:375, 1931. Montgomery, B. E.: ibid. **28**:374, 1931.

2. Norton, J. F., and Novy, M.: Am. J. Pub. Health **21**:1117, 1931.

3. Each of the three women subjects was sensitive to some protein: no. 1 to butternuts; no. 2, who had marked asthma, to pollens and fish; no. 3 to an unknown food protein.

thoroughly. The hands of the subject were carefully washed, rinsed and dried. When the skin had regained its normal moisture, the finger tips were placed lightly on the surface of the plate, not more than 2 fingers per plate. Care was taken not to crack the agar, although this occasionally happened. The fingers were left in contact with the agar surface for five minutes. The greatest care was taken that the hands in no way came in contact with any drug, but no effort was made to keep the washed skin free from bacteria. After the imprints were made the plates were incubated for twenty-four hours at 37.5 C., as experience had shown that further incubation did not visibly alter

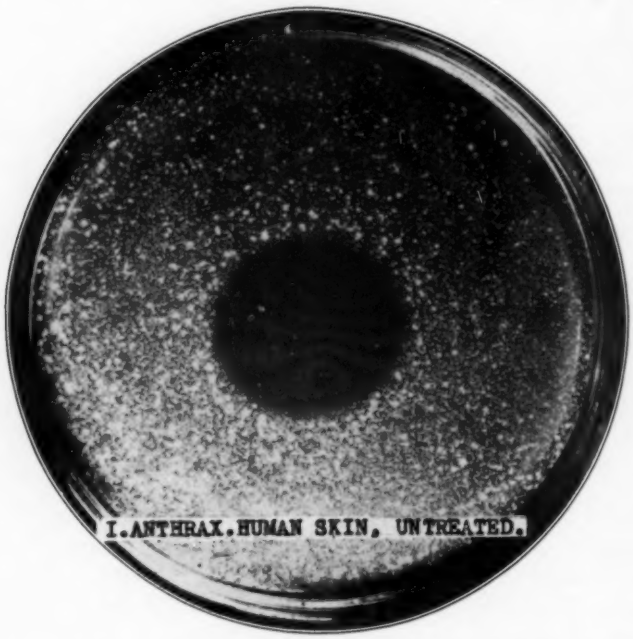

Fig. 1.—Agar plate, seeded with ninety day anthrax spores and showing a zone of inhibition on and around a print of normal human skin, left in contact with the inoculated plate for five minutes. Photograph taken after twenty-four hours of incubation at 37.5 C. A transfer, made five days after inoculation from the center of the clear zone, was sterile.

the results. After incubation the plates invariably showed numerous fine colonies of bacteria, evenly distributed throughout the medium, except in cases in which inhibition was observed. In such cases there were sharply outlined zones of inhibition entirely free from any colonies of the test organisms, as shown in figures 1 and 2. These zones extended not only throughout the depth of the agar, but also laterally for varying distances beyond the area of the fingerprints. Transfers

for the sterility of such zones of inhibition were made by cutting out a piece of agar from the center of the zone with a platinum loop and subculturing this agar in broth. Such tests, made with every type of organism used, including anthrax spores, were almost always sterile.

In some cases a heaping up of colonies was seen at the limits of the prints in cases showing no inhibition. In cases of inhibition, this same concentration of growth was frequently observed, not at the edge of the clear area, but slightly beyond it, with a narrow zone of apparently normal growth between this denser ring and the bacteria-free

Fig. 2.—Result of an experiment exactly similar to that shown in figure 1, but made on a different date. The zone of inhibition extends only slightly beyond the fingerprint.

area. Overgrowth of other than the test organism was observed on fingerprints on both inhibited and uninhibited plates. These overgrowths of organisms present on the skin, in cases in which inhibition of the test organism was present, indicated in another way the selective action of the skin, which will be described later.

The possible influence of pressure on the growth of the plates was controlled by contacts with glass stoppers and with fingers encased in rubber gloves. Such contacts gave no inhibitions. With the pressure factor relatively the same in all tests, it seems improbable that this had

any significance in the tests in which inhibition was observed. The fact that when inhibition was present it extended below and often laterally far beyond the actual area of contact with the skin would seem to preclude the possibility of some physical or mechanical action attributable merely to the contact of the skin with the agar. Moreover, this factor was the same in all tests, regardless of the observations. Although the hands were carefully rinsed, controls were made with a small amount of soap left on the skin, but no inhibition was obtained.

OBSERVATIONS

All the inhibition tests are summarized in table 1. This table shows that by this method definite inhibition of bacterial growth may occur,

TABLE 1.—*Summary of All Tests of Inhibition of Normal Human Skin*

Organism	Total No. of Tests per Person	Number of Inhibition Zones Found: Female 1	Female 2	Female 3	Male 1	Male 2	Male 3	Total Number of Tests	Total Inhibitions: Number	Total Inhibitions: Per Cent
Staphylococcus aureus										
Old	30	2	1	8	5	11	4	180	31	17.2
New	30	1	0	2	0	5	2	180	10	5.5
B. prodigiosus	30	0	0	2	2	16	9	180	29	16.1
B. pyocyaneus	30	0	0	1	3	4	0	180	8	4.4
Proteus	30	2	0	0	1	0	0	180	3	1.6
Colon group										
Escherichia no. 3	15	1	0	2	1	6	0	90	10	11.1
Escherichia no. 4	15	7	3	7	1	7	5	90	30	33.3
Aerobacter no. 8	10	0	0	0	0	2	2	60	4	5.5
Aerobacter no. 9	10	0	0	0	0	2	2	60	4	6.6
Aerobacter no. 10	10	0	0	0	3	0	0	60	3	5.0
B. subtilis, spores	30	9	9	12	8	14	11	180	63	34.0
B. anthracis, spores	..	..	..	4	..	..	..	4	4	(100)
Total	240	22 (9.1%)	13 (5.4%)	38 (15.3%)	24 (10%)	67 (27.9%)	35 (15.4%)	1,444	199	13.7

but that such inhibition is far from constant. Thus, in 1,444 tests, inhibition was obtained in 199 instances or 13.7 per cent. Moreover, the action of the skin differed markedly with different organisms, varying, in the comparable series, from inhibition in 34 per cent of the tests with the gram-positive, spore-forming bacillus to inhibition of only 1.6 per cent of the tests with Proteus.

These variations in the action of skin on different organisms offer certain striking exceptions to the usual behavior of lethal agents on bacteria. Thus, with anthrax spores, tests made on four different days showed in all cases an actual killing of these spores, which are notably resistant to other lethal agents. Although the number of tests with anthrax spores was small, these observations were confirmed with the gram-positive, sporulated bacillus, with which more inhibitions were obtained than with any other organism. Inhibition was noted in 63 cases, or 34 per cent of the 180 tests done with this organism, while with all the vegetative forms studied, the incidence of inhibition was

lower. With one exception, a colon group bacillus, Escherichia no. 4, which was inhibited in one third of its tests, there was a striking difference between the spore-forming and the vegetative cells, none of which, with this one exception, was inhibited in more than 17.2 per cent of the tests. The results with skin inhibition, therefore, in regard to spores and vegetative cells, are exactly the opposite of those noted with the usual chemical and physical means of disinfection. The strains used in this study have been carefully tested to be sure that they are not atypical in this respect.

In regard to the vegetative forms, the most resistant was Proteus. Bacillus pyocyaneus paralleled in these tests its known high resistance to chemical disinfection. Within the colon group of bacilli the similarity to chemical disinfection was close. It has been shown by one of us (Hill) that varieties of the genus Escherichia, that is, B. coli and closely related forms, are much more influenced by chemicals than those of the genus Aerobacter, that is, B. lactis-aerogenes and similar organisms. In the present study, the two Escherichia strains tested were inhibited in 40 cases, or 22.2 per cent of the tests. There was, however, a sharp difference between the two strains. With the three Aerobacter strains, the results were uniform, but the incidence of inhibition, 6 per cent, was much lower than in the case of Escherichia strains. Marked difference between the two strains of Staphylococcus aureus was noted, as the old strain was inhibited in 31 cases, or 17.2 per cent of the tests, while the strain freshly isolated from a furuncle was inhibited only 10 times, or in 5.5 per cent of the tests. It would be interesting to determine the relation, if any, between the incidence of inhibition and the virulence of an organism.

In regard to the variations of different individuals, there were 240 comparable tests made by each of the 6 subjects. The maximum incidence of inhibition for an individual was 27.9 per cent; the minimum, 5.4 per cent. The women inhibited in 15.5, 9.1 and 5.4 per cent of their tests; the men in 27.9, 15.5 and 14.5 per cent. The total number of cases of inhibition, therefore, was 69, or 9 per cent of the 720 tests made by women, and 123, or 17 per cent of the same number made by men.

Tests were made with the 10 fingers of a subject on the same day to determine possible differences in them. The results are summarized in table 2. These figures represent the maximum width and length of the zones of inhibition. It is probable that there is a mathematical relation between the area of the print, the number of organisms and the amount of inhibition, but until we have some method of measuring the variable amounts of inhibitory substance present, this cannot be determined.

In view of Fleming's [4] work on the bacteriolytic element or lysozyme which he was able to demonstrate in many different tissues, we performed a number of tests to demonstrate any possible lytic action of normal human skin. Fleming, working with Micrococcus lysodeikticus, an organism particularly susceptible to lysis, reported that a 1:100 skin extract gave an incomplete lysis of the test organism in one hour, a small degree of lysis as compared with the action of tears, nasal mucus and some other substances tested. Fleming and Allison [5] believe that the difference is not due to a different lysozyme in different tissues but to quantitative variations. We tried a few experiments by Fleming's method, i. e., putting a thin layer of agar over a plate that had been inoculated the day before, and making fingerprints on top of the second

TABLE 2.—*Diameters of Zones of Inhibition*

	Right Hand, Cm.	Left Hand, Cm.
Thumb	3.2 × 3.6	3.3 × 4.4
Forefinger	3.0 × 3.1	2.9 × 3.0
Middle finger	3.0 × 3.1	3.2 × 3.5
Fourth finger	3.3 × 3.4	2.8 × 3.2
Little finger	3.2 × 3.3	3.3 × 3.6

TABLE 3.—*The Bacteriolytic Action of Normal Human Skin*

Organism	Total Number of Tests	Complete Lysis	Partial Lysis	No Lysis
Gram-positive spore former (B. subtilis)	23	1	2	20
Staphylococcus aureus (2 strains)	24	1	0	23
B. prodigiosus	48	1	4	43
Escherichia	6	0	0	6
Aerobacter	2	0	0	2
	103	2	6	94
		1.9%	5.8%	

layer. After the second incubation of such plates, readings were difficult when the skin inhibited growth in the top layer, without lysing colonies in the lower layer. We therefore preferred to make fingerprints directly on incubated plates, as this in no way altered the appearance of the plates except when lysis occurred. Our experiments on lysis are reported in table 3.

It is seen from table 3 that the presence of a lytic substance in the skin was rare. In 103 tests, with 5 organisms, complete lysis was obtained only three times, twice with the spore-forming bacillus and once

4. Fleming, A.: Proc. Roy. Soc., London, s. B, **93**:306, 1922. Fleming, A., and Allison, V. D.: Brit. J. Exper. Path. **3**:252, 1922. Fleming, A.: Lancet **2**:217 (Feb. 2) 1929.

5. Fleming, A., and Allison, V. D.: Proc. Roy. Soc., London, s. B, **94**:142, 1922-1923.

with B. prodigiosus (fig. 3). There were 6 cases of partial lysis, in which there was a definite diminution of the number of colonies, but without complete disappearance of the growth. Fleming and Allison [5] believe that lysis due to the action of a lysozyme is not attributable to a phage. It is interesting to note that the skin may on a given day kill the bacteria present in an unincubated plate, but at the same time be unable to dissolve colonies of the same organism. Whether the skin has at least two types of action on bacteria or the difference is only quantitative can only be conjectured at this time.

No evidence was obtained of any variations during the two menstrual cycles covered by these experiments, although Fisher [6] has made some

Fig. 3.—Bacteriolysis. The plate had been seeded with B. subtilis spores, incubated for eighteen hours, after which the entire plate showed heavy growth. The fingertip was left in contact with the surface of the culture for five minutes, and the plate was again incubated for eighteen hours, after which a perfectly clear zone was found, extending slightly beyond the print and through the depth of the medium.

observations in regard to this aspect of the problem. It seems that a much larger series would have to be studied before definite conclusions could be drawn. If an increase of inhibitive action was shown during menstruation, the observation might well be correlated with the work of Macht and Lubin [7] on the menotoxin.

6. Fisher, V.: Proc. Soc. Exper. Biol. & Med. **28**:952, 1931.
7. Macht, D. I., and Lubin, D.: J. Pharmacol. & Exper. Therap. **22**:413, 1924.

SUMMARY

1. In 1,444 tests made with 6 subjects on twelve types of bacteria, the skin inhibited the growth of bacteria in 199 cases, or 13.7 per cent. Bactericidal action was frequently demonstrated.

2. The skin varied greatly in its action on different types of bacteria. Its action was most marked on the gram-positive, spore-forming bacilli; less on the staphylococci and gram-negative bacilli tested.

3. Marked differences were also observed in the subjects used for the tests, the incidence of inhibitory action varying from 5.4 to 27.9 per cent.

EFFECT OF VARIOUS ANESTHETICS ON THE CHOLESTEROL AND SUGAR CONTENT OF THE BLOOD

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In the course of experimentation on gallstone formation,[1] it was noted that animals under ether anesthesia showed a higher blood cholesterol value than they did preceding the anesthesia. The literature on this point was in some respects meager, and was conflicting. Therefore, experiments were carried out in an attempt to determine the amount and the extent of change in blood cholesterol under various anesthetics.

Bloor [2] reported a rise in blood fat (in which all the lipoid constituents shared) of from 40 to 100 per cent in dogs under ether anesthesia. The rate of rise was most marked during the first hour. Using chloroform, Bloor found no rise in blood cholesterol unless the dog was previously stuffed with fat. Then there was a sharp rise. He noted an "after rise" from chloroform two or three days later. Both morphine and ethyl alcohol produced a slight or no increase in blood cholesterol, but did produce an after rise two or three days later. Reicher [3] obtained a rise in blood cholesterol in dogs up to 300 per cent under ether anesthesia, and found the same results with chloroform. He reported morphine as producing a slight rise. According to Bürger and Schweisheimer,[4] acute alcohol poisoning in the dog causes an increase in the blood cholesterol which appears only after the amount of alcohol in the blood decreases. There is no distinct lipemia at any time. Ducceschi [5] subjected dogs to ether anesthesia for periods of from sixty to ninety minutes daily and found a marked rise in blood cholesterol. Similar experiments with chloroform showed a slight rise during the first two or three days, and then a decrease daily to below normal. Mann [6] found an initial increase in blood cholesterol in dogs anesthetized with ether, followed by a decrease, after an hour or so of anesthe-

From the Department of Pathology, the University of Chicago.

1. Hospers, C. A.: The Experimental Production of Gallstones, with a Review of the Literature, Arch. Path. **14**:66 (July) 1932.
2. Bloor, W. R.: J. Biol. Chem. **19**:13, 1914.
3. Reicher, K.: Ztschr. f. klin. Med. **15**:235, 1908.
4. Bürger and Schweisheimer: Ztschr. f. d. ges. exper. Med. **5**:136, 1916.
5. Ducceschi, V.: Arch. di farmacol. sper. **27**:118, 1919.
6. Mann, F. C.: Some Bodily Changes During Anesthesia, J. A. M. A. **67**: 172 (July 15) 1916.

sia, below the values taken as normal and then a gradual increase on further etherization. Mahler [7] found that in man ether anesthesia produced a continuous rise in blood cholesterol proportional to the duration of the anesthesia. His longest period of anesthesia was one hundred minutes. He found no rise under nitrous oxide-oxygen anesthesia. Lattes [8] found no rise from chloroform anesthesia. Manceau [9] reported a slight rise in the blood cholesterol of monkeys from both chloroform and nitrous oxide anesthesia. Ginesty [10] found the blood cholesterol lower after barbital anesthesia than it was beforehand. However, no determinations were made during narcosis. Recently, Gray [11] reported a definite rise in blood cholesterol after three weeks of repeated administrations of chloroform.

TECHNIC

Both dogs and rabbits were used in the experiments. Avoiding excitement as much as possible, the dogs were tied on their backs to an operating table. The femoral vein was exposed under 2 per cent procaine hydrochloride anesthesia. The dogs were kept quiet by petting and if excited were quieted for from twenty to forty minutes before the experiment proceeded. Approximately 1 cc. of blood was drawn from the exposed vein, twice in succession, and both samples were run in duplicate as normal blood cholesterol values. Ether anesthesia was instituted by the use of the ordinary closed dog mask attached to an ether bottle. The amount of ether given was kept constant, varying only with each dog initially, and in most instances producing complete relaxation without loss of the corneal reflex. One cubic centimeter of blood was drawn at intervals varying from every few minutes to every half hour. All samples were run in duplicate. The ether experiments in dogs covered periods of anesthesia up to ten hours. Rabbits were treated in the same manner except that they were placed in ordinary rabbit boxes and blood was drawn from the ear vein without local anesthesia. The ether was administered through a similar smaller apparatus. Anesthesia was continued for from four to six hours. Sackett's modification [12] of Bloor's method was used for the determination of the blood cholesterol values. This method requires but 0.25 cc. for each determination, so that the amounts of blood used eliminated any great hemorrhage factor. The total cholesterol of the whole blood was determined. In the experiments

7. Mahler, A.: J. Biol. Chem. **69**:653, 1926.
8. Lattes, L.: Arch. f. exper. Path. u. Pharmakol. **66**:132, 1911.
9. Manceau, P.: Compt. rend. Soc. de biol. **92**:1507, 1925.
10. Ginesty, Lassalle and Mériel: Compt. rend. Soc. de biol. **91**:1399, 1924.
11. Gray, S. H.: J. Biol. Chem. **87**:591, 1930.
12. Sackett, G. E.: J. Biol. Chem. **64**:203, 1925.

in which the blood sugar was measured also, an extra cubic centimenter of blood was drawn each time for the sugar determinations. Byrd's [13] modification of the Folin method for the determination of blood sugar was employed, with the additional modification that 1 cc. of blood was used instead of 0.1 cc., and other solutions in corresponding amounts.

Experiments with chloroform were conducted in a similar manner, this anesthetic being substituted for ether in the ether bottle. Animals were anesthetized for as long as ten hours. Similar experiments were performed under nitrous oxide and ethylene anesthesia, using an apparatus to which was attached an ordinary dog mask containing an expiratory valve. Anesthesia was continued for from four to six hours with ethylene, and up to nine hours with nitrous oxide.

DATA

1. *Blood Cholesterol.*—Ether Anesthesia in Rabbits: The experiment was performed on six rabbits. The blood cholesterol values taken as normal varied from 60 to 96 mg. per hundred cubic centimeters of blood. Blood was drawn every fifteen or thirty minutes after the initiation of ether anesthesia. The changes in blood cholesterol values are shown in chart 1, on which is represented the amount of change from the normal value for each rabbit. The results of three typical experiments are charted, together with an average curve of the changes in all six rabbits averaged for each time period. It will be noted that the blood cholesterol began to rise rapidly with the advent of anesthesia and continued to do so for from forty-five to sixty minutes. Continued anesthesia was not accompanied by a further rise, but the hypercholesteremia began to decrease somewhat less rapidly than it rose, and then more slowly continued to drop toward normal, reaching it after about four hours of anesthesia. The peak of hypercholesteremia, then, is seen to occur after approximately one hour of anesthesia, the amount varying from 38 to 100 mg. above the normal.

Ether Anesthesia in Dogs: Ten dogs were used. The values taken as normal ranged between 130 and 150 mg. per hundred cubic centimeters of blood. In five dogs ether anesthesia was slowly induced to such a degree as to produce complete relaxation but not to such an extent as to abolish the corneal reflex (surgical anesthesia). The amount of ether given was then kept constant. Blood was drawn as before. Three typical examples of the blood cholesterol changes are illustrated on chart 2*a*; the values represent the changes from the normal as determined for each dog. The blood cholesterol was found to fluctuate more than in rabbits, but a similar change is seen. A peak in the hypercholesteremia occurs after from thirty to ninety minutes

13. Byrd, T. L.: J. Lab. & Clin. Med. **2**:67, 1925.

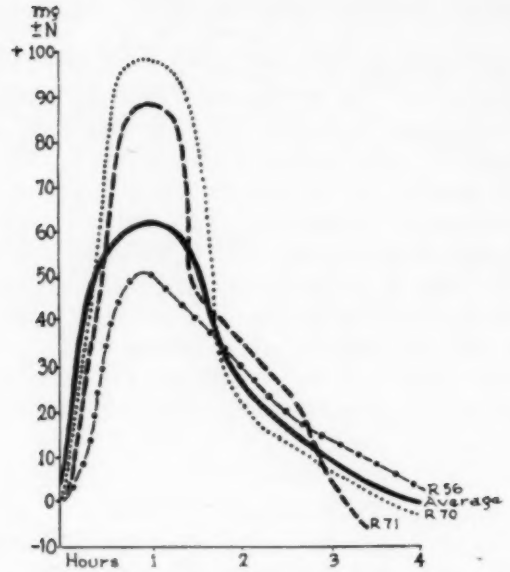

Chart 1.—Changes in the blood cholesterol of rabbits under ether anesthesia.

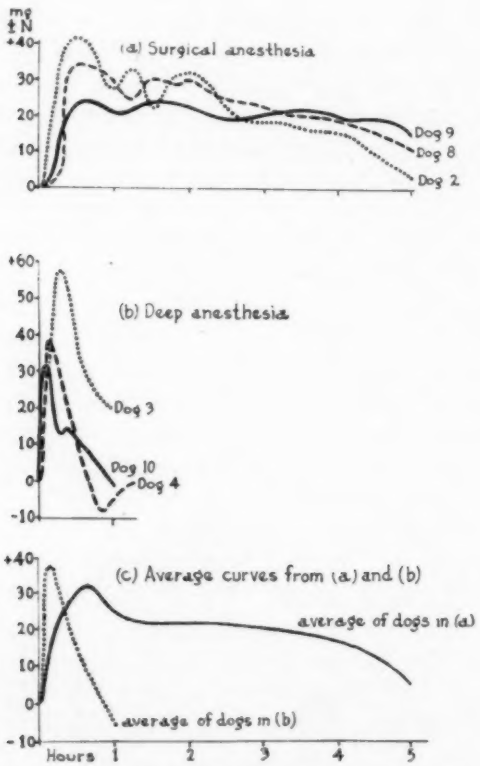

Chart 2.—Changes in the blood cholesterol of dogs under ether anesthesia.

of anesthesia; then a gradual return toward the normal, approaching it after about five hours of anesthesia. This is best illustrated by plotting a curve from the average of all five dogs for each time period, chart 2*c*. The change from normal is less in dogs than in rabbits, the highest point of hypercholesteremia varying from 18 to 42 mg. The blood cholesterol was found to be sensitive to amounts of ether given. If, at any point during the experiment, the amount of ether was increased, a rise in the blood cholesterol followed. This is illustrated in chart 3 by the terminal rise in dogs due to an increase in the rate of anesthesia to kill the animals, and by the secondary rise in blood cholesterol after an increase in the depth of anesthesia in both dogs and rabbits. Other examples are included in the later section on changes in the blood sugar.

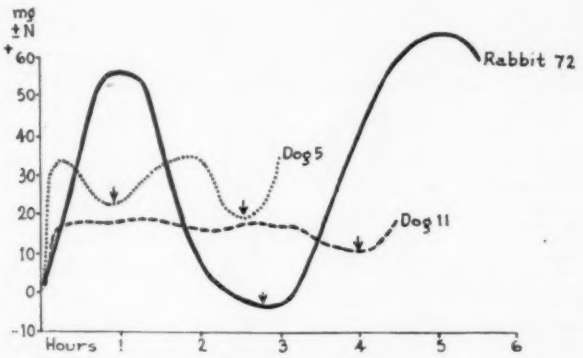

Chart 3.—Changes in the blood cholesterol due to increasing the rate of anesthesia (arrows indicate point of increase).

In three dogs the anesthesia was given much more rapidly, larger amounts of ether being given to produce rapid and deep anesthesia. Chart 2*b* shows a more rapid rise than in surgical anesthesia, a peak being reached in from five to ten minutes, and a more rapid drop toward normal, which is reached after about an hour of anesthesia. The average of these dogs shows a higher peak as well as a more rapid change.

Two dogs subjected to smaller quantities of anesthetic, so that only partial relaxation was obtained and reflexes were very active, showed a much lower peak and much more fluctuation.

Chloroform Anesthesia: Eight dogs were used. Again three typical experiments are illustrated (chart 4), together with the composite curve averaged from the changes in all eight dogs. The values taken as normal ranged from 127 to 200 mg. per hundred cubic centimeters of blood, some of which are probably higher than the true normal for the dogs. If determinations were made during the first

few minutes of anesthesia, the blood cholesterol was found to fluctuate somewhat, even falling below the values taken as normal, especially if it was rather high. The curves are plotted, using fifteen minutes after the introduction of anesthesia as the initial point of change. A gradual, continuous rise in the blood cholesterol occurred, proportional to the length of anesthesia. Three dogs allowed to recover after the experiment showed a continuing rise in blood cholesterol for at least twenty-

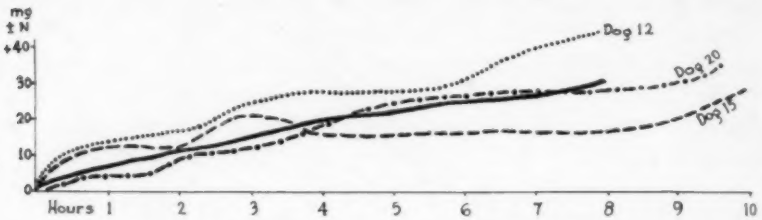

Chart 4.—Changes in the blood cholesterol of dogs under chloroform anesthesia. The heavy black line shows the average for eight dogs.

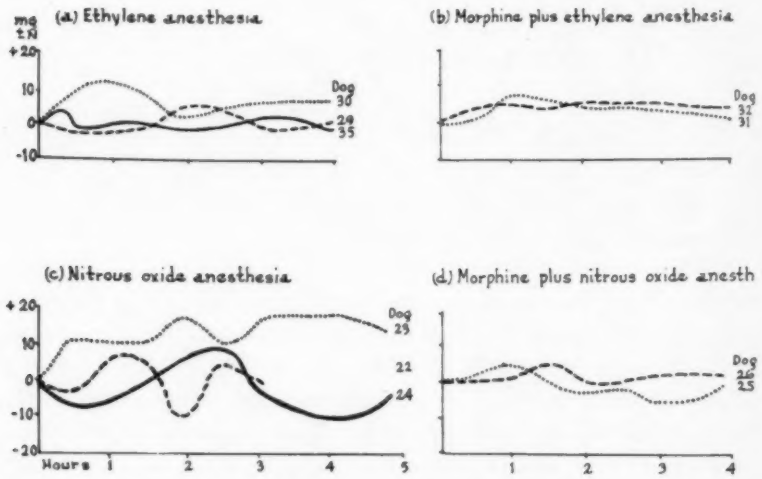

Chart 5.—Changes in the blood cholesterol of dogs under (*a*) ethylene, (*b*) morphine plus ethylene, (*c*) nitrous oxide and (*d*) morphine plus nitrous oxide anesthesia.

four hours. After a week, however, the values were down to normal limits. Table 1 gives the essential figures for one of these experiments.

Ethylene and Nitrous Oxide Anesthesia: Ethylene-oxygen anesthesia alone was found to be rather poor for dogs. It was somewhat difficult to secure a state of good relaxation, and a concentration of 95 per cent ethylene to 5 per cent oxygen was required. Five dogs

were used. The results in three are charted (chart 5) for the first four hours. There was no great change in the blood cholesterol at any period, but a moderate fluctuation was constant. Two dogs given 30 mg. of morphine sulphate subcutaneously about half an hour before the experiment showed much less fluctuation (chart 5*b*).

Nitrous oxide-oxygen anesthesia was found to be even less satisfactory as an anesthetic for dogs; 95 per cent nitrous oxide to 5 per cent oxygen was used. It was difficult to abolish voluntary movements

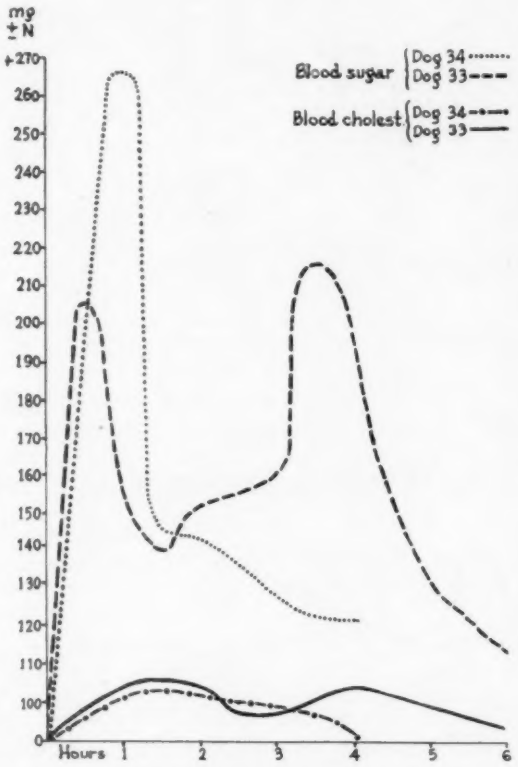

Chart 6.—Changes in the blood sugar and blood cholesterol under ether anesthesia.

TABLE 1.—*Changes in Blood Cholesterol in Chloroform Anesthesia (Dog 16)* *

		Cholesterol, Mg. per 100 Cc.
5/12/31: 1:10 p.m.	Normal blood cholesterol	216
7:45 p.m.	After 6½ hours of chloroform anesthesia	240
5/13/31: 7:30 p.m.	Twenty-four hours after anesthesia	253
5/19/31: 2:25 p.m.	One week after anesthesia	206

* A black male terrier; weight, 10.9 Kg.

and almost impossible to secure complete relaxation. The fluctuations were greater than with ethylene (chart 5*c*), but here, too, there was no great or constant change in the blood cholesterol. Morphine, given beforehand, diminished the fluctuation markedly and resulted in a minimal change from the normal (chart 5*d*).

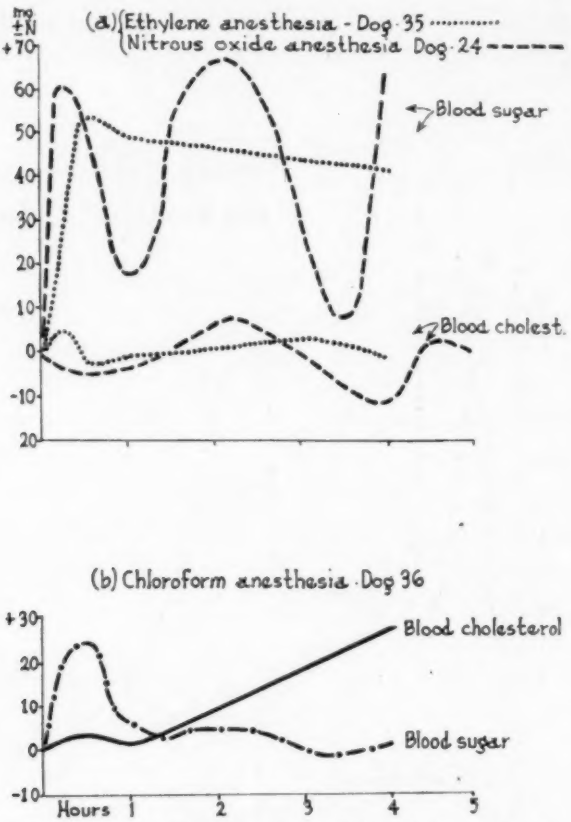

Chart 7.—Changes in the blood sugar and blood cholesterol under (*a*) ethylene and nitrous oxide anesthesia, and (*b*) chloroform anesthesia.

Excitement: As has been indicated, some of the changes in blood cholesterol were thought to be due to something other than the anesthetic. On numerous occasions blood drawn when the animal was excited from tying, etc., showed higher cholesterol values than succeeding samples taken after the dog had been quiet for some twenty-five minutes. These changes are shown in table 2. Table 3 shows the changes taking place in a dog before and after excitement from playing and fighting. Excitement was accompanied by a hypercholesteremia

TABLE 2.—*Effect of Excitement on the Blood Cholesterol of Dogs*

Dog	Time		Cholesterol, Mg. per 100 Cc.	Rise, Mg. per 100 Cc.
4	1:30 p.m.	Blood drawn from quiet dog	148	12
	1:55 p.m.	Dog excited by presence of cat; then tied down without any attempt at quieting	160	
18	10:40 a.m.	Dog tied to table, causing excitement; blood drawn immediately afterward	210	10
	11:55 a.m.	Blood drawn after quieting dog since 10:40	200	
28	9:00 a.m.	Dog tied to table; excited; blood drawn	213	11
	9:25 a.m.	Blood drawn after quieting dog	202	

TABLE 3.—*Effect of Excitement on Blood Sugar and Blood Cholesterol in Dog 37* *

Date	Time		Sugar, Mg. per 100 Cc.	Change, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Change, Mg. per 100 Cc.
12/4/31	9:05 a.m.	After playing excitedly for about one hour	141	29	157	10
	10:15 a.m.	After lying quiet for one hour	112		147	
12/5/31	1:00 p.m.	After spending a morning alone in a quiet room	97	55	142	17
	2:30 p.m.	After a fight with another dog, preceded by playing for ½ hour	152		159	
12/7/31	6:50 p.m.	After being alone in a quiet room all afternoon	105	32	139	9
	7:30 p.m.	Following 30 min. of tumbling play, pulling, jumping, etc.	137		148	
12/8/31	9:30 a.m.	Following 20 min. of play	131	26	153	6
	11:50 a.m.	After quiet of two hours	105		147	

* A pet terrier, very lively but trained to obey. The dog was fed on a diet of meat and bread once a day, in the evening after the completion of the experimentation.

TABLE 4.—*Effect of Excitement on Blood Cholesterol of Rabbits*

Rabbit	Time (10/6/31)		Cholesterol, Mg. per 100 Cc.	Change, Mg. per 100 Cc.
74	2:05 p.m.	Put in box; rather quiet		
	2:15 p.m.	Blood taken	85	
	2:27 p.m.	Blood taken	85	
	2:36 p.m.	Blood taken	83	
			(Average, 84)	
	2:40 p.m.	Removed from box; placed before dogs, chased about, rolled onto back, rolled over and over, etc., for 20 minutes		
	3:00 p.m.	Blood taken	93	8 (rise)
75	3:05 p.m.	Chased about cage, run about floor, rolled, etc., for 15 minutes		
	3:20 p.m.	Blood taken	93	
	3:25 p.m.	Blood taken	93	
	4:20 p.m.	Blood taken	88	
	4:40 p.m.	Blood taken	85	8 (drop)
3-76	4:30 p.m.	Taken from cage and put in box quietly		
	4:45 p.m.	Blood taken	80	
	5:00 p.m.	Blood taken	76	
			(Average, 78)	
	5:05 p.m.	Taken from box; thrown into air, chased (not caught) by a dog, rolled over and over on floor many times, etc., until 5:35 p.m.		
	5:40 p.m.	Blood taken	89	
	5:50 p.m.	Blood taken	88	10 (rise)

averaging about 10 mg. above the normal. Table 4 illustrates similar changes in rabbits with relation to excitement.

2. *Blood Sugar.*—Ether Anesthesia: On two dogs the changes in blood sugar were followed with the blood cholesterol changes. Chart 6 illustrates the changes in the two blood constituents. The blood sugar rose rapidly to reach a peak within the first hour of anesthesia, and then gradually fell toward normal. The blood cholesterol, changing much less, showed a slightly slower but similar response. Dog 33 also illustrates the effect of changes in the depth of anesthesia. After one and a half hours of anesthesia, the amount of ether being given was slightly increased. At the end of three hours of anesthesia, the ether bottle was refilled, resulting in a temporary increase in the amount of anesthesia given. The corresponding rise in both blood sugar and blood cholesterol values is apparent.

Other Anesthetics: Under chloroform anesthesia the change in blood sugar was similar to that under ether: a rapid rise and a gradual fall to normal, in spite of the fact that the blood cholesterol continued to rise (chart 7*b*). Under ethylene and nitrous oxide anesthesia the blood sugar showed the same rapid rise, with subsequent fluctuation about this elevated point (chart 7*a*).

Excitement: Table 3 demonstrates the rise in blood sugar after excitement not related to anesthesia.

COMMENT

Mann[6] suggested that the initial rise in blood cholesterol under ether anesthesia might be due to excitement. Excitement must play some part in the hypercholesteremia. Lyons[14] has recently reported an emotional hypercholesteremia in cats: an increase in blood cholesterol of from 25 to 30 per cent after from twenty to forty minutes of excitement. This change was absent after the removal of the sympathetic nervous system. But this factor does not seem to be entirely responsible. The excitement stage under all the anesthetics used was similar, yet the rise of blood cholesterol under ether was greater than under the others. Then, too, excitement without anesthesia produced less change than occurred with the anesthesia. Dog 11 (chart 3) received barbital before the ether anesthesia. Excitement was eliminated, and the rise was less marked but not absent. Dog 4 (table 2) was anesthetized immediately after the excitement experiment, and by comparison with chart 2*b* it will be seen that ether anesthesia was accompanied by a greater hypercholesteremia than occurred with excitement in the same dog.

14. Lyons, C.: Am. J. Physiol. **98**:156, 1931.

The fact that blood sugar rises under anesthesia is well established. All authors do not agree as to the type of change. Macleod [15] thought that the changes in the dextrose content of the blood from anesthesia were slight. Ross and McGuigan [16] stated the increase in blood sugar to be general and consistent, and demonstrated a continuance of the high sugar content of blood after the cessation of anesthesia. Their periods of anesthesia lasted two hours. Examination of their tables shows some values still rising after two hours, but others have already reached a peak at one hour and are lower after two hours. The after rise may be associated with excitement as consciousness returns. Sansum and Woodyatt,[17] working with phlorizinized dogs, found an initial increase in blood sugar with ether and with chloroform, followed by a fall. Nitrous oxide failed to produce such changes. Mahler [7] reported a continuous rise in blood sugar under ether anesthesia for periods of one hundred minutes. Mackay and Dyke [18] found a rapid initial rise, with a gradual return to the original level. Trout [19] has reported a postoperative increase in blood sugar after twenty minutes of ethylene anesthesia.

The cause of the hyperglycemia is still more disputed. In 1910, Macleod and Pearce [20] demonstrated a reduction in the glycogen content of the liver following ether anesthesia. Shaffer [21] thought that the rise in sugar was due to excitement and asphyxia, but King, Moyle and Haupt [22] had previously eliminated asphyxia by producing the anesthesia by intravenous injection of ether, and still obtained a hyperglycemia. Ross and McGuigan [16] felt that the effect was not due to excitement or asphyxia but to the ether itself acting as an activator on liver glycogen, permitting the action of diastase on it. However, Stewart and Rogoff,[23] working with adrenalectomized rabbits, found a greater increase in blood sugar from asphyxia superimposed on ether anesthesia than from the anesthesia alone. Ross and Davis [24] suggested that ether hyperglycemia might be due to depression of the internal secretion of the pancreas, and Mahler [7] used this theory to explain the absence of the rise in blood sugar on the subcutaneous injection of

15. Macleod, J. J. R.: Diabetes: Its Pathological Physiology, New York, E. Arnold, 1913, p. 187.
16. Ross, E. L., and McGuigan, H.: J. Biol. Chem. **22**:407, 1915.
17. Sansum and Woodyatt: J. Biol. Chem. **21**:1, 1915.
18. Mackay, R. L., and Dyke, S. C.: Brit. J. Anæsth. **6**:61, 1928.
19. Trout, H. H.: Anesth. & Analg. **8**:269, 1929.
20. Macleod, J. J. R., and Pearce, R. G.: Am. J. Physiol. **27**:341, 1910-1911.
21. Shaffer, P. A.: J. Biol. Chem. **19**:297, 1914.
22. King, Moyle and Haupt: J. Exper. Med. **16**:178, 1912.
23. Stewart, G. N., and Rogoff, J. M.: J. Pharmacol. & Exper. Therap. **15**:238, 1920.
24. Ross, E. L., and Davis, L. H.: Am. J. Physiol. **53**:391, 1920.

insulin previous to anesthesia. Fuss [25] believed ether hyperglycemia due to mobilization of sugar from the liver. Rosenthal and Bourne [26] found that hepatic function was diminished after anesthesia, and Cantarow and Gehret [27] cited clinical material demonstrating that patients with hepatic disease do not show a rise in blood sugar under ether as other patients do.

It seems most probable that the hyperglycemia is due to increased hepatic glycogenolysis. Ether itself must play a part in this process, since it is accompanied by a rise so markedly greater than that of excitement alone. The hyperglycemia occurring in chloroform, ethylene and nitrous oxide anesthesia is much less in amount and may very well be due to excitement, which alone can lead to a rise in blood sugar equal to that from these anesthetics. It has been shown that in ether anesthesia the changes in blood sugar and in blood cholesterol tend to parallel each other. Then, if the change in blood sugar is due to increased mobilization from the liver, may not at least part of the increased amount of cholesterol in the blood have the same origin?

Insulin prevents the rise of both these blood constituents under anesthesia. Remesow and his co-workers [28] have recently found that while cholesterol leads to glycogenolysis in the liver, cholesterol plus insulin results in the storage of glycogen in the liver. In anesthesia the effect may be due, as stated, to a suppression of the internal secretory function of the pancreas, and if insulin is given artificially it may nullify the glycogenolysis by its power to increase storage.

However, the hypercholesteremia cannot be attributed entirely to loss of lipoid from the liver. Other organs also release cholesterol into the blood. Manceau [9] reported a considerable diminution in the cholesterol content of the adrenal gland from chloroform anesthesia. After the administration of ethyl alcohol to dogs over a period of days, Ducceschi [29] found a constant decrease in the cholesterol content of the adrenal gland averaging 40 per cent, and sometimes a decrease in other organs, such as the testis.

The gradual drop in hypercholesteremia after an hour's anesthesia may be due to the gradual lowering of the amount of cholesterol easily separated from the tissues. Since ether does not produce much toxic

25. Fuss, H.: Klin. Wchnschr. **9**:410, 1930.

26. Rosenthal, S. M., and Bourne, W.: The Effect of Anesthetics on Hepatic Function, J. A. M. A. **90**:377 (Feb. 4) 1928.

27. Cantarow, A., and Gehret, A. M.: Ether Hyperglycemia, J. A. M. A. **96**:939 (March 2) 1931.

28. Remesow and Matrossowitsch: Ztschr. f. d. ges. exper. Med. **77**:67, 1931. Remesow, Matrossowitsch and Sepalowa: ibid. **77**:100, 1931.

29. Ducceschi, V.: Arch. ital. de biol. **70**:93, 1920.

degeneration, cholesterol from that source is not liberated, and as removable cholesterol diminishes in the tissues, the blood cholesterol falls to or below normal.

The change in the cholesterol content in chloroform anesthesia is more easily explained. The initial changes are of the same magnitude as the changes with excitement, and may be attributed to that factor (dog 18, table 2). The gradual but continuous rise in blood cholesterol with continuous chloroform anesthesia is, perhaps, the result of toxic degeneration of the liver cells with liberation of the lipoid substances, increasing in amount as the destruction of the tissue proceeds. In 1909, Howland and Richards [30] suggested this as the cause of the after rise of blood lipoids following chloroform poisoning.

The fluctuations in blood cholesterol found throughout ethylene and nitrous oxide anesthesia are of the same magnitude as those produced by excitement and, as with the hyperglycemia, may be attributed entirely to it, especially since these gases fail to produce a good anesthetic state in the dogs. The diminution of the fluctuations when morphine precedes the anesthesia also indicates that excitement is the main factor in the changes.

Although it was known that ether anesthesia is attended by a hypercholesteremia, Mann [6] alone noted that this is temporary and is followed by a drop to normal under continued anesthesia. He attributed the rise to excitement. This report gives evidence that although excitement is a factor, ether itself is responsible for a transient but not continued hypercholesteremia, and that the more generally known changes in blood sugar are proportional to the lipoid changes. Chloroform anesthesia has been reported as producing no rise (Bloor [2] and Lattes [8]), a slight rise (Ducceschi [5] and Manceau [9]) and a great rise (Reicher [3]) in acute experiments. An after rise has been found constantly. The experiments in this paper show an absence of immediate change but a gradual, continuous rise proportional to the length of anesthesia. The after rise is also noted. Under nitrous oxide anesthesia, Manceau [9] found a slight rise in the blood cholesterol of monkeys. According to Mahler,[7] patients previously given morphine showed no rise in blood cholesterol under nitrous oxide. The data here presented show no changes due to nitrous oxide. An investigation of the literature revealed no studies of the blood cholesterol under ethylene anesthesia. This report indicates that ethylene has no effect on the blood cholesterol.

The differences in previously reported results on changes in blood sugar and blood cholesterol under various anesthetics can be attributed largely to a factor seldom considered, that of excitement. Shaffer [21] and Mann [6] suggested that excitement affected the blood sugar, and Lyons [14]

30. Howland, J., and Richards, J.: J. Exper. Med. **11**:344, 1909.

showed for the first time (1931) that emotion disturbed the blood cholesterol. The experiments reported in this paper demonstrate that excitement in rabbits and dogs causes both a hyperglycemia and a hypercholesteremia, and that the excitement seems to be responsible for the changes in blood sugar and the acute changes in blood cholesterol under chloroform, nitrous oxide and ethylene anesthesias.

Chloroform and ether anesthesia disturb the lipoid metabolism, and ether affects the carbohydrate metabolism as well. Nitrous oxide and ethylene—of more import because of its wider applicability—disturb neither lipoid nor carbohydrate metabolism, and seem therefore to be more physiologic anesthetics.

SUMMARY

1. Continuous ether anesthesia in dogs and rabbits is accompanied by a hypercholesteremia that, in ordinary surgical anesthesia, reaches a peak in from sixty to ninety minutes and thereafter gradually diminishes in amount, returning to approximately normal limits in from four to five hours.

2. Continuous chloroform anesthesia is accompanied by slight immediate change but by a gradual and continuous rise in the blood cholesterol proportional to the duration of anesthesia (up to ten hours).

3. Ethylene and nitrous oxide anesthesias are accompanied by no changes in the blood cholesterol other than those explainable by excitement and imperfect anesthesia.

4. Excitement is accompanied by a hypercholesteremia. This factor increases, but is not entirely responsible for the change found under ether anesthesia. It seems to be responsible for initial changes under chloroform and for the irregularity in the blood cholesterol values under ethylene and nitrous oxide.

5. Ether anesthesia is also accompanied by a hyperglycemia that frequently tends to be proportional to the hypercholesteremia. Chloroform, ethylene and nitrous oxide anesthesia are accompanied by a hyperglycemia, as is excitement without anesthesia.

6. Ethylene and nitrous oxide, as anesthetics, seem to be more physiologic in their action than ether and chloroform.

FIFTIETH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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CONGENITAL DEFORMITIES

Congenital Malformations of the Hand.—Kanavel,[1] in two excellently illustrated monographs, presented the complex group of congenital malformations of the hand. From a review of the literature and of his own cases he concluded that the cases were usually hereditary, and that they arose from a defect or an injury to the germ plasm. He illustrated the common types and discussed their treatment in detail. Any one attempting plastic surgical procedures in these cases should be thoroughly conversant with Kanavel's technic.

Congenital Dislocation of the Hip.—Dickson[2] divided congenital dislocations of the hip into three groups according to the age in which they occur: (1) those occurring in patients less than 4 years of age, (2) those occurring in patients between 4 and 9 years and (3) those

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This report of progress is based on a review of 177 articles selected from 337 titles appearing in the medical literature approximately between July 30, 1932, and Nov. 21, 1932. Only the papers that seemed to represent progress have been selected for review.

1. Kanavel, A. B.: Congenital Malformations of the Hands, Arch. Surg. **25**:1 (July); 282 (Aug.) 1932.

2. Dickson, F. D.: Surg., Gynec. & Obst. **55**:81, 1932.

occurring in patients over 9 years. He expressed the belief that in the majority of cases in patients under 4 years of age the dislocation can be reduced by a closed manipulation, but that occasionally open reduction is necessary. It is his opinion, further, that congenital dislocation of the hip in children older than 4 years should usually be treated by open operation, that many of the dislocated hips in children between 4 and 9 years can be reduced, and that in some of the children beyond this age the hips can be successfully restored to their normal position. Many of the hips, however, require some other type of operation, and he advocates the shelf operation for the older children. He outlined his technic for this operation. Preceding the operation, he applies skeletal traction for two weeks. Briefly, a wide anterior approach is used. A shelf which extends well anteriorly and posteriorly is turned down from the ilium just above the head of the femur. A wedge of bone is taken from the region of the anterior superior spine and wedged between the shelf and the ilium. The entire operation is performed under traction, which is maintained for six weeks afterward. In 21 of 26 shelf operations, he obtained good results; 2 patients were improved, and in 3 the operations were failures.

POLIOMYELITIS

Early Diagnosis and Treatment of Poliomyelitis.—Macnamara and Morgan,[3] as a result of their experience in the treatment of infantile paralysis, concluded that it is possible to diagnose poliomyelitis in the preparalytic stage. In their cases, the preparalytic stage lasted from two to seven days; rarely was the onset fulminating. The use of human immune serum gave excellent results. They insist on the importance of examining the cerebrospinal fluid at the bedside of the patient, so that serum can be administered immediately if the diagnosis is positive. The initial dose of serum was 50 cc., part being given intrathecally and part intravenously. If the dose was adequate, the temperature fell and the general condition improved. If improvement was not marked within eighteen hours, the dose was insufficient, and from 20 to 40 cc. more was injected intravenously. Of the series of 133 patients, 7 only, in their opinion, were not benefited; they attributed these failures to insufficient dosage, or to the delay between the withdrawal of the cerebrospinal fluid and the administrations of the serum.

Poliomyelitis, a Preliminary Report of 98 Cases.—During the 1931 epidemic of poliomyelitis, 98 patients were studied by Kramer[4] in the Jewish Hospital, Brooklyn. Ninety per cent of the cases were in chil-

3. Macnamara, J., and Morgan, F. G.: Lancet **1**:469 (Feb. 27); 527 (March 5) 1932.

4. Kramer, B.: New York State J. Med. **32**:855, 1932.

dren less than 10 years of age. A diagnosis was made in 54 cases before paralysis appeared. The incidence of paralysis in patients treated with convalescent serum was certainly not less than that in the untreated patients. The Drinker respirator was used in 10 cases. The author concluded that the respirator is of value only in the spinal type of paralysis, and not in the bulbospinal or the bulbar type. Forty-six, or 47 per cent of the patients, recovered completely.

[ED. NOTE.—Any new treatment passes through a stage of enthusiastic support before a correct appraisal of its value is secured. The present opinion regarding the use of convalescent serum seems to be somewhat less optimistic than formerly.]

Epidemic of Poliomyelitis.—Peck [5] made a statistical report of the 1931 epidemic of poliomyelitis in New York State; 4,080 cases were reported from July 1 to Nov. 1, 1931. Seventy-six per cent of the patients received treatment in a hospital. Eleven per cent of the patients died, whereas in 1916, 27 per cent died. Paralysis developed in only 17, or 0.5 per cent of the patients treated in hospitals for contagious diseases during the preparalytic stage. Boys were affected more often than girls. Fifty-three per cent of the patients were under 5 years of age; 31 per cent were under 10 years, and only 3 per cent were over 20 years. The majority of persons affected were born after the 1916 epidemic. This, the author thought, spoke for generalized acquired immunity. Only 6 of the 4,080 cases could be considered to be caused through contact.

TUBERCULOSIS

Tuberculous Spondylitis Treated at Bamelwerd, Germany, Between 1912 and 1930.—Reinhart [6] reviewed the cases of 91 patients with tuberculosis of the spine, 74 of whom had been discharged or had died and 17 of whom were still under treatment at the time of writing. Most of the lesions were in the lower dorsal part of the spine or in the upper lumbar part. The twelfth dorsal vertebra was most frequently involved. In 42 per cent of the cases the disease began in patients between the ages of 16 and 25. Forty-seven per cent of the patients were in the first two decades of life. Fifty-six of the 91 patients (61 per cent) had abscesses. Men (74.5 per cent) were affected more often than women. Thirty per cent of all the patients observed and 50 per cent of those with abscesses had fistulas; half of the fistulas had followed surgical incision. Deformity was present in 54 of the 91 patients (59 per cent). Lesions from the seventh dorsal to the second lumbar vertebra caused the worst deformities. The

5. Peck, H. T.: New York State J. Med. **32**:854, 1932.
6. Reinhart, M.: Beitr. z. Klin. d. Tuberk. **79**:745, 1932.

severest types were seen in female patients and in patients in whom the condition started in childhood. Pulmonary lesions were present in 22 patients (24 per cent). Extrapulmonary lesions were found in 20 of the 91 patients (22 per cent). In 16 of these 20, the spinal lesion and the other lesion appeared simultaneously. Renal tuberculosis and glandular tuberculosis were the commonest. Tuberculous exposure in the family was noted in 38 cases, or 41 per cent. The sedimentation time was determined in 15 uncomplicated cases; in 9 the results were normal. Of 21 patients with abscesses, 13 showed marked acceleration of the sedimentation time, and only 2 had a normal rate. All varieties of treatment were employed, but mainly conservative. In 12 patients, spinal fusions were performed. The author was of the opinion that the statistics of the deformity and mortality were unaltered by the operations in these few cases. The conditions of the 72 patients who were discharged were as follows: clinically healed, 47 (55.3 per cent); improved, 10 (13.9 per cent), and unimproved, 11 (15.3 per cent). Four patients died at the hospital (5.5 per cent). Of twenty-six patients with closed abscesses, 4 (15 per cent) died. The author agreed with Calot that scalpel opening causes a catastrophe. Of the 58 patients still living, 46 were capable of full work; 8 were capable of limited labor, and 4 were incapable of labor.

Culture of Tubercle Bacilli from Blood According to Löwenstein's Method in Tuberculosis of the Bones.—Urgoiti,[7] following in a general way the method devised by Löwenstein, attempted to culture tubercle bacilli from the blood of patients suffering from tuberculosis of the bones. A tuberculous bacillemia was believed to be present in cases in which there was active tuberculosis. The author described in detail the technic used. In 26 of 67 cases of tuberculosis of the bones, cultures of tubercle bacilli were recovered from the blood. There were 10 positive cultures in 20 cases of pulmonary tuberculosis.

Tuberculous Bacillemia.—Gualdi [8] used the method of Löwenstein in attempting to isolate tubercle bacilli from the blood of patients who were suffering from various forms of tuberculosis. A number of studies were also made on patients with rheumatic infections. The author was able to obtain only 1 positive culture of tubercle bacilli in 30 tuberculous patients. All of the blood cultures in cases of rheumatic infection were negative. The difficulty of isolating tubercle bacilli from the blood was stressed. The author did not feel that his results indicated the absence of tuberculous bacillemia.

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7. Urgoiti, A.: Beitr. z. Klin. d. Tuberk. **80**:480, 1932.
8. Gualdi, A.: Policlinico (sez. chir.) **39**:493, 1932.

[Ed. Note.—The recovery of tubercle bacilli from the blood in tuberculosis of the bones and joints is of considerable importance and stresses the importance of both general and local measures in treatment.]

Roentgen Signs of Tuberculosis of the Vertebral Body.—Daub and Badgley [9] studied the roentgen appearance of the vertebral body in 100 cases of tuberculosis of the spine. They were able to distinguish three types of lesions: a central type, an intervertebral articular type and an anterior type. The central type showed the lesion in the midportion of the vertebral body. Infection occurred most probably through the posterior spinal arteries. This was the usual type observed in children. It was more common in the dorsal region. Collapse of the vertebral body and severe deformity were observed chiefly in this type. The intervertebral articular type of infection probably occurred through the epiphyseal arteries. The infection was chiefly on the disk side of the vertebral body. Here a spread to the intervertebral disk occurred early with rapid narrowing of the disk, while the vertebral body remained intact until late. This type was more common in the lumbar region. In the anterior type the infection was along the anterior surface of the vertebral body. The infection probably spread through the intercostal arteries. The author found narrowing of the intervertebral disks to be the earliest and most constant sign of vertebral tuberculosis. Abscess was the most common complication, occurring in 84 per cent of the cases. Double lesions with intervening normal vertebrae were found in 10 per cent of the patients. Tuberculosis in other parts of the body was seen in 52 per cent of the patients. Pulmonary tuberculosis was present in 24 per cent of the patients.

[Ed. Note.—Several of the editors have observed these three types of vertebral lesions in tuberculosis, but they have considered the central type to be the least common, especially in children.]

PYOGENIC INFECTIONS

Maggots in Osteomyelitis.—Buckman and Blair [10] carried on Baer's method of treatment of osteomyelitis by means of maggots, with certain modifications. Their work has contributed definitely to the clinical and laboratory technic and to the knowledge concerning this procedure. They concluded that maggots do not eat, destroy or remove dead bone, and that for this reason operative treatment should be adequate. They suggested that the proliferation of healthy granulation tissue is due to the mechanical stimulation of the incessantly crawling maggots. They concluded that the treatment, though more costly, is not so time-con-

9. Daub, H. P., and Badgley, C. E.: Am. J. Roentgenol. **27**:827, 1932.
10. Buckman, J., and Blair, J. E.: Surg., Gynec. & Obst. **55**:177, 1932.

suming as dakinization and is superior to the "Orr technic" in that healing takes place more rapidly, gives better scars and does not, as a rule, necessitate prolonged periods of immobilization in plaster of paris.

Pathologic Fractures in Osteomyelitis.—Capener and Pierce [11] called attention to the not infrequent occurrence of fractures following osteomyelitis, and stated that at the University of Michigan this complication had occurred in 1.66 per cent of 1,086 cases, and that the fractures represented one third of all pathologic fractures of the long bones. Delayed recognition of the disease with subsequent diaphyseal sequestration, long-standing atrophy from disuse and overzealous removal of bone when "saucerizing" a cavity were considered the chief causes of such fractures. The authors emphasized the importance of preventing these disasters by splinting the extremity during convalescence.

[ED. NOTE.—In view of the frequency of pathologic fracture in osteomyelitis, it is important to emphasize that the presence of the disease is not incompatible with healing of the fracture. Union has been obtained by prolonged splinting in the experience of several of the editors.]

NEOPLASMS

Skeletal Metastases in Hypernephroma.—Lehmann,[12] in an exhaustive review of the Germanic literature on metastasis in hypernephroma, called attention to several important aspects of the problem. It was Helferish who in 1887 reported metastases to the bone as the first symptom of a silent tumor of the kidney, occurring long before the primary renal tumor occasioned any attention. The occurrence of such distant metastases, often solitary for a long time, has led to their excision, sometimes with the impression that they were primary tumors of the bone, and sometimes with a knowledge of their true character. If the solitary metastasis and the primary tumor of the kidney are both excised, life in certain cases may be definitely prolonged. In a follow-up study of 9 patients so treated, the duration to death was found to be one year in 1, one and one-half years in 1, two years in 3, from five to six years in 3 and twelve years in 1. The author believes that at least one third of the cases of metastases from hypernephroma were cases of solitary metastasis at first. He was inclined to attribute the frequency of metastasis to the flat bones to the narrowness of the capillaries in the red marrow present in the flat bones of the adult.

Osteitis Fibrosa.—Lang [13] stated that osteitis fibrosa is a secondary condition of the bone dependent on circulatory disturbances in bones

11. Capener, N., and Pierce, K. C.: J. Bone & Joint Surg. **14**:501, 1932.
12. Lehmann, W.: Arch. f. klin. Chir. **170**:331, 1932.
13. Lang, F. J.: Am. J. Path. **8**:263, 1932.

following either trauma without tearing of the periosteum or functional bending and cracking of the skeleton because of insufficient calcification (rickets, scurvy and osteomalacia). Occasional occurrence of osteitis fibrosa associated with tumors of the parathyroid gland does not contradict the concept which regards osteitis fibrosa as a secondary process in bone dependent on osseous circulatory disturbances.

[Ed. Note.—The concept that osteitis fibrosa and giant cell tumors are due to functional circulatory disturbances is not new. Of great importance, however, is the emphasis placed on the occasional but not constant association of osteitis fibrosa and tumors of the parathyroid gland.]

Giant Cell Tumor.—Kirklin and Moore [14] reviewed the roentgen appearance in 86 proved cases of giant cell tumor and classified them into two types: 1. The first was the usual variety described in all textbooks as a central tumor situated most often in the end of a long bone, exhibiting trabeculation and expanding, but not breaking through the cortex. 2. "Trabeculation was conspicuously absent. The roentgenograms gave evidence of homogenous lysis of the affected area: the cortex was not only expanded but was dissolved wholly or in part, and the tumor projected into the soft tissues. This variety might be mistaken for primary sarcoma or a massive metastatic growth."

Roentgen Treatment of Giant Cell Tumor.—Pfahler and Parry [15] reviewed the roentgen treatment of giant cell tumors in 26 cases; 1 patient was reported as being the first one (1906) ever to be treated in this way. They concluded that fractional dosage with high voltage roentgen rays is the method of choice and is superior to surgical intervention or to a combination of the two. All of their patients gave a satisfactory response, and none died of a malignant process.

Peirce [16] reported 2 cases of apparent malignant degeneration of giant cell tumors. He agreed with Pfahler and Parry as to the treatment.

[Ed. Note.—Opinion is still divided as to the relative merits of irradiation and operation in the treatment of giant cell tumors. Cure by irradiation requires a longer time and necessitates prolonged observation of the patient.]

Diseases of the Bone After Roentgen Treatment for Uterine Carcinoma.—Philipp [17] reported a series of observations on the patho-

14. Kirklin, B. R., and Moore, C.: Am. J. Roentgenol. **28**:145, 1932.
15. Pfahler, G. E., and Parry, L. D.: Am. J. Roentgenol. **28**:151, 1932.
16. Peirce, C. B.: Am. J. Roentgenol. **28**:167, 1932.
17. Philipp, E.: Strahlentherapie **44**:363, 1932.

logic changes which occurred in the femora after roentgen and radium therapy for carcinoma of the uterus. There was a gradual decalcification particularly in the necks of the femora which, the author was convinced, was not due to metastases. He suggested that a change in the blood vessels as a result of the large amount of irradiation probably played a rôle in the decalcification. Five cases were reported in detail. In 1 case, coxa vara developed on both sides. In 2 cases, fracture of the femoral neck was observed. Fracture of the neck of the femur was seen on both sides in 1 case. In the fifth case, there was a loss of cartilage in the hip joint, with stiffening of the joint after irradiation; no inflammatory lesion could be demonstrated in the hip. These changes occurred from two to nine months after irradiation. The author could find no similar reports in the literature. He believed that poorer technic in the past led to less rapid changes, and that the patients usually died of metastasis before such conditions could be recognized. The relation of these findings to medicolegal cases was discussed.

Reaction of Muscle Tissue to Tumor.—Leadingham's [18] photomicrographs demonstrated the apparent stimulation and elongation of the nuclei of striated muscle by contiguous neoplastic tissue. The nuclei, or muscle corpuscles, increased in number and apparently extended through the sarcolemma in spite of concomitant atrophy and degeneration of the muscle fibers. Sokolow and Fujunami were quoted as having made similar observations. A biologic stimulation of the muscle corpuscles seemed to occur owing to the presence of the neoplastic tissue, and these corpuscles entered into the neoplasm.

[Ed. Note.—A practical inference may be drawn, namely, that when muscle is involved by a neoplasm, wide and careful excision of the contiguous muscle tissue must be done.]

THE BACK

Reduced Lumbosacral Joint Space.—Of a series of 80 patients with signs of sciatic irritation studied by Williams,[19] 79 per cent had narrowing of the lumbosacral disk as shown by roentgenograms. Anteroposterior roentgenograms were taken with the hips flexed and the lumbar spine flattened. In most cases there was a history of sudden strain with pain in the lower part of the back. Confinement to bed brought temporary relief only. Subsequent attacks were accompanied by pain radiating down the course of the sciatic nerve on one or both sides, corresponding chiefly to the distribution of the fifth lumbar nerve.

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18. Leadingham, R. S.: Am. J. Cancer **16**:556, 1932.

19. Williams, P. C.: Reduced Lumbosacral Joint Space: Its Relation to Sciatic Irritation, J. A. M. A. **99**:1677 (Nov. 12) 1932.

Twelve patients had only symptoms in the lower part of the back without radiating pain. The author believes that the probable cause of this condition was rupture of the nucleus pulposus. Congenital narrowing of the disk is considered unlikely, as no evidence of such a condition was found in 300 roentgenograms of persons in early life. The rupture is believed to have been the result of continued physiologic trauma on an intrinsically weak region. The root pain is believed to have been due to changes following the rupture rather than to the rupture itself. Constriction of the intervertebral foramina followed loss of the joint space. This produced compression of the fifth lumbar nerve segment. Another source of nerve irritation was a hypertrophic fringe resulting from abnormal stresses following the loss of the intervertebral space. The treatment indicated was fixation of the lumbosacral joint either by conservative measures or by operation.

[ED. NOTE.—We believe that Williams has made a contribution in calling attention to the narrowed lumbosacral joint space. The weakness of his paper lies in the fact that he did not exclude other lesions producing symptoms in this region.]

CHRONIC ARTHRITIS

Ferment Theory of Arthritis.—Podkaminsky [20] suggested that the immediate cause of arthritis deformans lies in a disturbance of the activities of the ferments of the synovial fluids. This disturbance causes the accumulation of materials which interferes with the normal absorbing and secreting activities of the synovial lining of the joint. The intra-articular cartilage therefore is poorly nourished, its elasticity suffers, and chronic trauma affects the subchondral bone and soon leads to proliferative changes. In the development of spondylitis deformans the nucleus pulposis plays the part of the joint cleft, while the disks and the end-plates play the part of the joint cartilage.

[ED. NOTE.—In this as well as in previous papers the author's theories and experimental studies are of interest in attempting to explain the early physiologic disturbances. Unfortunately, so far they are only theories.]

Knotty Articulations of the Fingers.—Hissard [21] reported 19 cases of articular enlargement of the fingers. The patients had a fusiform swelling of the interphalangeal and metacarpal-phalangeal joints resembling that seen in cases of chronic atrophic arthritis. The photographs accompanying the article could certainly be considered to be those of the hands of patients suffering from atrophic arthritis. Twelve of the

20. Podkaminsky, N. A.: Arch. f. klin. Chir. **171**:592, 1932.
21. Hissard, M.: Ann. de dermat. et syph. **3**:806, 1932.

19 patients had hereditary syphilis, 6 probably had it, while 1 did not have sufficient stigmas to make the diagnosis probable. While the gross appearance of the hands was identical with that seen in chronic atrophic arthritis, the resemblance ended there. There was no pain in the joints on active or passive motion. Motion was limited only slightly. There was no deformity or disalinement of the joints. The patients were unable to state when the condition appeared, and some were not aware of it until it was called to their attention. None of the patients, however, were under 15 years of age. The roentgenograms taken in 5 cases showed no abnormalities. There did not seem to be any connection between the condition of the patients and the chronic rheumatism sometimes seen in hereditary syphilis. This condition was confined to the fingers. There were no general symptoms, fever, pain or roentgenographic changes elsewhere in the skeleton. The beginning of the condition was not known, although various factors, such as the onset at puberty and findings suggestive of acromegaly, led the author to the hypothesis that the "knotty arthritis" might be due to endocrine disturbances secondary to hereditary syphilis.

Disturbances of Growth in Chronic Arthritis in Children.—These disturbances were studied by Kuhns and Swaim,[22] who believe that they are due chiefly to the involvement of the proliferating epiphyseal cartilages by the arthritis, resulting in early ossification. Three types of involvement of growth were noted: persistence of infantile proportions in the hands and feet, shortness of an extremity or a portion of an extremity and, rarely, dwarfism. These sequelae emphasized the need for meticulous management of the young arthritic patient.

[ED. NOTE.—This condition is probably more common in the arthritides of childhood than is commonly appreciated.]

Monarticular Arthritis, Simulating Tuberculosis.—From March, 1924, to January, 1930, Smith [23] encountered 24 cases of monarticular arthritis in which an accurate diagnosis could not be made after a careful study of the history, the results of physical examination, the roentgenograms, the analysis of the blood and the tests with tuberculin. Biopsy and inoculations into guinea-pigs were necessary to establish a diagnosis. Even at biopsy it was not possible to rule out tuberculosis on the gross appearance of the synovial membrane. Careful study of the microscopic sections and inoculations into guinea-pigs or cultures furnished the only accurate diagnostic criteria.

(To be Concluded)

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22. Kuhns, J. G., and Swaim, L. T.: Disturbances of Growth in Chronic Arthritis in Children, Am. J. Dis. Child. **43**:1118 (May, pt. 1) 1932.

23. Smith, A. D. DeF.: Monarticular Arthritis Simulating Tuberculosis: A Clinical and Pathologic Study of Twenty-Four Cases, Arch. Surg. **25**:54 (July) 1932.